

The Role of Emotional Processing in Psychotherapy for Depression: An Integrative Neurophysiological- Psychological Approach

Thesis (Cumulative Thesis)

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by Nadja Ilona Dörig

Accepted in the Spring Term 2014 on the Recommendation of the Doctoral Committee:

Prof. Dr. phil. Martin Grosse Holtforth (main advisor)

Prof. Dr. rer. nat. Boris. B. Quednow

Prof. Dr. rer. nat. Björn Rasch

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“Changing emotions with emotions”
— Leslie S. Greenberg —

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Summary

Cognitive-Behavioral Therapy (CBT) is an effective treatment for major depressive disorder (MDD). However, response rates are still far from satisfying. As CBT for depression aims at changing dysfunctional and maladaptive processes on the cognitive and the emotional level, it seems surprising that the role of emotional processing has received relatively little attention in the past. In the current thesis, an integrative neurophysiological-psychological approach is pursued, suggesting that increased knowledge about therapy-related emotional processes might lead to new strategies in favor of better outcomes. First of all, emotional processing was studied as a possible psychological mechanism of change during psychotherapy for depression by deliberately fostering emotional processing in the course of CBT. In a further step, the role of emotional processing on a neural level in healthy participants and depressed patients was investigated using individualized self-critical stimuli as a trigger for emotional and cognitive responses and exploring its links to psychotherapy outcome. Self-criticism is a psychological construct that involves constant and harsh criticism and demands on the self and that is normally accompanied by negative self-referent feelings such as guilt, failure, or self-hate.

The current work consists of three studies all contributing to the further understanding of emotional processing in order to progress towards more efficacious, substantial, and individualized treatment strategies for people suffering from MDD.

The first study (manuscript I) aimed at evaluating the efficacy of Exposure-Based Cognitive Therapy (EBCT-R) in a randomized-controlled trial comparing CBT with EBCT-R. Results showed that emotional processing in the second phase of EBCT-R was predictive of better therapy outcome, thereby underpinning the role of emotional processing as a crucial mechanism of change in psychotherapy for depression.

In the second study (manuscript II) we investigated the neural correlates of self-criticism in a group of healthy participants. Functional magnetic resonance imaging (fMRI) results revealed that self-criticism activated a large subcortical network reflecting essential emotional processing, as well as frontal and midline brain networks involved in self-referential processing and cognitive control.

Finally, the third study (manuscript III) was designed to investigate neurophysiological alterations during confrontation with self-critical stimuli in depressed patients compared to healthy control participants. Moreover, we examined links between neural response to emotional stimuli and therapy outcomes. Results yielded enhanced subcortical responses, yet no frontal alterations in depressed patients as compared to healthy control participants. In addition, we identified amygdala activity to self-critical stimuli as a possible biomarker of treatment response. Right amygdala reactivity was negatively associated with symptom improvement at therapy end, as well as three months thereafter. Furthermore, these relationships were mediated by emotional but not by cognitive mechanisms of change.

In the last section, results of the three studies are integrated in an overall discussion, including implications for clinical practice and directions for future research. Taken together, the results from psychotherapy process research and from the fMRI findings converge on the notion that dealing productively with disturbed emotions might be a key factor of successful therapy outcome in psychotherapy with depressed patients.

Zusammenfassung

Die kognitive Verhaltenstherapie (KVT) ist bei der Behandlung von akuten Depressionen erwiesenermaßen wirksam. Die Psychotherapie bei Depressionen zielt auf die Veränderung dysfunktionaler Prozesse auf kognitiver und emotionaler Ebene ab. Daher ist es erstaunlich, dass die Rolle der emotionalen Verarbeitung in der KVT als Prozessmechanismus bis heute nur ungenügend untersucht wurde. Das Ziel der vorliegenden Arbeit besteht darin, potentielle Möglichkeiten zur Steigerung der Erfolgsquote von Psychotherapie bei Depressionen zu identifizieren, indem neue Erkenntnisse über die neurophysiologische und psychologische Verarbeitung emotionaler Prozesse gewonnen werden. Hierzu wurde ein integrativer neurophysiologisch-psychologischer Ansatz verfolgt. In einem ersten Schritt wurde die emotionale Verarbeitung als Prozessmechanismus im Rahmen einer kontrolliert-randomisierten Vergleichsstudie untersucht. In einem weiteren Schritt wurde die Verarbeitung von Selbstkritik auf neuronaler Ebene mit Hilfe von funktioneller Magnetresonanztomographie (fMRT) bei gesunden und depressiven Personen erfasst. Pathologische Selbstkritik ist ein psychologisches Konstrukt, welches mit hohen selbstbezogenen Ansprüchen verbunden ist und in der Regel von negativen Gefühlen wie Schuld, Versagen, oder Selbsthass begleitet wird.

Die vorliegende Arbeit umfasst drei Studien zur emotionalen Verarbeitung auf psychologischer und neuronaler Ebene. Der gemeinsame Nenner liegt in dem Bestreben Ideen für effektivere, nachhaltigere, und möglicherweise individualisierte Therapiestrategien zur Behandlung von Depressionen zu gewinnen.

In einer ersten Studie, welche den Rahmen der vorliegenden Arbeit liefert (Manuskript I), untersuchten wir die Wirksamkeit und die Wirkweise einer weiterentwickelten Form der KVT, der Expositionsbasierten Kognitiven Therapie (EBCT-R), welche zusätzlich Interventionen zur Förderung der emotionalen Verarbeitung integriert. Die Ergebnisse dieser kontrolliert-randomisierten Therapiestudie zeigten, dass die emotionale Verarbeitung während der zweiten Phase der EBCT-R ein besseres Therapieergebnis vorhersagte. Dies unterstreicht die Rolle der emotionalen Verarbeitung im Rahmen der KVT als wichtiger Veränderungsmechanismus in der Psychotherapie von Depressionen.

In einem zweiten Schritt (Manuskript II) untersuchten wir funktionelle kognitive und emotionale Netzwerke als Reaktion auf individuelle selbstkritische Stimuli in einer Gruppe von gesunden Probanden mittels fMRT. Die Ergebnisse der bildgebenden Analysen zeigten, dass Selbstkritik ein ausgedehntes subkortikales Netzwerk aktivierte, welches eine vertiefte emotionale Verarbeitung widerspiegelte. Des Weiteren zeigten die gesunden Probanden bei der Konfrontation mit selbstkritischem im Vergleich zu neutralem Material erhöhte neuronale Aktivierungen in Strukturen, welche mit der Verarbeitung selbstbezogener Stimuli sowie mit einer erhöhten kognitiven Kontrolle in Beziehung stehen.

In einer weiteren Studie (Manuskript III) interessierten uns neurophysiologische Veränderungen der kognitiven und emotionalen Informationsverarbeitung nach Konfrontation mit selbstkritischen Stimuli bei depressiven Patienten im Vergleich zu gesunden Kontrollpersonen. Zusätzlich gingen wir der Frage nach, ob die neuronale Aktivität als Reaktion auf einen emotionalen Stimulus im Zusammenhang mit dem Therapieerfolg stehen könnte. Im Vergleich zu gesunden Kontrollpersonen zeigten depressive Patienten eine erhöhte neuronale Aktivierung in verschiedenen subkortikalen Regionen. Die Resultate zeigten jedoch keine Auffälligkeiten in frontalen Hirnregionen. Des Weiteren zeigte sich eine negative Korrelation zwischen der neuronalen Aktivität in der rechten Amygdala und der Symptomverbesserung direkt nach der Therapie sowie drei Monate nach Therapieende. Dieser Zusammenhang wurde von emotionalen, jedoch nicht von kognitiven Veränderungsmechanismen vermittelt.

Im letzten Kapitel werden die Resultate der drei Studien in eine Gesamtdiskussion integriert sowie im Hinblick auf mögliche praktische Implikationen und weiterführende Forschung diskutiert. Zusammengefasst weisen sowohl die Ergebnisse der Psychotherapie-Studie als auch der fMRT-Analysen darauf hin, dass eine erfolgreiche Auseinandersetzung mit gestörten emotionalen Prozessen essentiell für den Erfolg einer Psychotherapie der Depression ist.

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1. Introduction

The following work was conducted in order to improve psychological treatments for patients suffering from major depressive disorder. With focus on emotional processing and using information about neurophysiological processing using functional magnetic resonance imaging (fMRI) and psychometric data over time, we set out to explore new ways to enhance response rates of psychological treatments for depression. The following questions will lead you throughout this work:

- Does fostered emotional processing enhance response rates of psychotherapy for depression?
- Is emotional processing linked to psychotherapy outcome?
- Is self-criticism a valuable trigger for studying cognitive and emotional neural responses?
- Do acutely depressed patients show alterations in cognitive and emotional information processing to self-critical stimuli compared to healthy control participants?
- Are alterations in emotional information processing of depressed patients linked to psychotherapy outcome?
- Which psychological processes are involved in the association between fMRI activity and treatment response?

Chapter 1 will give an overview of the theoretical background that is necessary for an integrative understanding of the present thesis.

1.1 Major depressive disorder

Major depressive disorder (MDD) is a disabling condition that adversely affects a person's social and occupational functions, sleeping and eating habits as well as general health. The most widely used criteria for diagnosing MDD in a research context are listed in the *Diagnostic and Statistical Manual of Mental Disorders IV* published by the American Psychological Association (APA; 2000). Depressive symptoms include primarily depressed mood and a loss of interest or pleasure in daily activities for more than two weeks. Low mood is often accompanied by low self-esteem, changes in appetite or weight, sleep disturbances, agitated or decreased motor activity, fatigue, feelings of worthlessness or inappropriate and excessive guilt, and troubles in thinking or concentrating. Furthermore, MDD patients often report thoughts about death and/or suicide. Tragically, the World Health Organization (WHO; 2012) estimates that suicide results in approximately one million deaths every year so that MDD could be seen as a life-threatening disease. Depending on the number and severity of symptoms, a depressive episode can be categorized as mild, moderate, or severe. Additionally, the course of the disorder varies widely and diagnosis depends on the presence of single, or in case of repeated episodes, recurrent MDD.

Depression is one of the most common mental disorders and the leading cause of disability worldwide with an estimated 350 million people affected (WHO, 2012). Epidemiological studies show that in most countries the lifetime prevalence for people who would suffer from a clinically depressive disorder lies between 8 and 12% with women having a greater risk for developing MDD than men (Kessler et al., 2005).

1.2 Efficacy of psychotherapy for depression

Systematic meta-analyses have shown that psychological interventions for treatment of depressive disorders are effective in inpatients (Cuijpers et al., 2011) as well as outpatients (Cuijpers et al., 2008; de Jong-Meyer et al., 2007). Furthermore, a meta-analysis comparing seven common psychological treatments, i.e., cognitive-behavioral therapy, nondirective supportive treatment, behavioral activation treatment, psychodynamic treatment, problem-solving therapy, interpersonal psychotherapy, and social skills training reported no large differences in efficacy between different forms of psychological treatments for mild to moderate depression (Cuijpers et al., 2008). Although psychotherapeutic treatment of depression seems to be efficacious, not every patient can benefit

from a therapeutic treatment and a large proportion of patients suffer a relapse after successful treatment termination. In a further meta-analysis of 28 studies, Vittengl and colleagues (2007) have estimated that about one third (29%) of the responders to an acute treatment of cognitive therapy will suffer a relapse/recurrence within one year without treatment continuation and even half of the responders (54%) will relapse within a two-year episode. These rates appear comparable to those associated with other depression-specific psychotherapies. While they are still significantly lower than those associated with pharmacotherapy, they are far from satisfying. Thus, one of the greatest challenges for psychotherapy research will be to optimize strategies for better response rates and more sustainable treatment.

Improving response rates and reducing recurrence creates a need to understand which variables predict negative or positive responses among those patients starting psychotherapy. Discovering which variables predict the outcomes of CBT/CT interventions has concerned depression research for a long time. However, as comprehensive reviews have shown, it seems to be hard to find robust predictors (Driessen & Hollon, 2010; Hamilton & Dobson, 2002). In a recent study (Jarrett et al., 2013) the authors conducted logistic regression-analyses of demographics, pre-treatment illness characteristics and psychosocial measures as well as therapeutic alliance at the midpoint and its relation to therapy outcome in a sample of 523 recurrent depressed outpatients. Controlling for symptom severity, they reported unemployment, history of only two depressive episodes, and greater social impairment before treatment, as well as a lesser understanding/use of cognitive therapy skills and less mid-phase symptom reduction as predictors of poor final outcome. Moreover, improvement in clinical symptoms in the early course of therapy generally points towards better treatment response (e.g., Stiles et al., 2003; Strunk, Brotman, & DeRubeis, 2010).

The identification of biomarkers may help to improve the prediction of response in psychotherapy. Especially potential functional and structural neural biomarkers using positron emission tomography or functional or structural magnetic resonance imaging are being investigated intensively for pharmacological as well as for psychological treatments (see Fu, Steiner, & Costafreda, 2013 for an overview). Nevertheless, no biomarkers for predicting response in depression treatment are currently used in clinical practice so far. In addition to improve response prediction, investigation of biomarkers of response in psychotherapy may also open new avenues for understanding mechanisms of change in depression treatment at neurophysiological as well as psychological levels. For more information about fMRI biomarkers of outcome in psychotherapy for depression see also manuscript III in chapter 2.

1.3 Self-criticism

1.3.1 Self-criticism and depression

Pathological self-criticism is a psychological construct that involves constant and harsh criticism and demands on the self, striving for high achievement and perfection, and chronic concerns about disapproval and rejection from others. This form of negative self-evaluation can be experienced in various aspects of the self, including interpersonal dimensions, appearance, behavior, thoughts and emotions, personality, and intellectual attributes (Blatt & Zuroff, 1992). Self-criticism is an often reported feature in depressed patients and especially related to feelings of failure, self-hate, guilt, and anhedonia (Luyten et al., 2007). Greenberg and colleagues (1998) have proposed that the harsh negative affect, which accompanies the self-criticism, might be the principal antecedent of states of depressive helplessness. Moreover, self-criticism is closely related to the neuroticism factor as a higher order trait characteristic (Clara, Cox, & Enns, 2003) and also related to the maladaptive and self-critical aspects of perfectionism (Dunkley, Zuroff, & Blankstein, 2006). Several studies have shown that clinically depressed populations exhibit higher levels of self-criticism than normal healthy controls (Klein et al., 1988; Luyten et al., 2007) and that levels of self-criticism are positively related to depressive symptoms and negatively related to global domains of psychosocial functioning (Dunkley et al., 2009). In addition, self-criticism has been associated with the recurrence of depressive episodes (Mongrain & Leather, 2006). Pronounced self-criticism is also related to poor psychotherapy outcome (Marshall et al., 2008; Rector et al., 2000) and there is growing evidence that self-critical patients might represent a challenge for therapists. Whelton and colleagues (2007) found a negative association between levels of self-criticism and clients' ratings of the working alliance with 169 clients attending a community clinic. Highly self-critical patients reported enhanced hostile mood states and less positive affect, possibly partly explaining the negative association between high levels of self-criticism and low alliance ratings. Two prominent theories from different perspectives have been suggesting that high levels of self-criticism or related constructs might also act as personality vulnerability for developing depression (Beck, 1983; Blatt et al., 1982).

Given these alarming findings, research on the construct of self-criticism has been gaining attention in the field of psychopathology and psychotherapy within the last years. At this point it is important to note that self-criticism is not an exclusive feature of depression. In a study of Luyten and

colleagues (2007), levels of self-criticism did not differ between depressed and mixed psychiatric patients, underpinning that self-criticism might be involved in a broad range of psychopathologies and act as a trans-diagnostic process (Shahar et al., 2012). Furthermore, several theories conceptualize self-criticism as a psychological phenomenon varying on a continuum from healthy to maladaptive aspects of experience (Blatt, 1974; Gilbert & Irons, 2005; Whelton & Greenberg, 2005). Hence, self-critical thinking as a conscious and realistic evaluation of oneself may constitute a healthy behavior and even facilitate striving for and achieving of important goals and standards.

1.3.2 Emotion in self-criticism

Cognitive models have traditionally viewed depressogenic self-criticism as variants of maladaptive, negative thoughts, or schemas which bias information processing (Abramson, Seligman, & Teasdale, 1978). Whelton and Greenberg (2005) studied a sample of healthy college students and split them into two groups reporting high versus low self-criticism respectively. Then they analyzed and rated videotapes where the students criticized themselves and responded to the criticism after an imagination exercise that recalled an experience of failure. Highly self-critical students were judged to be more contemptuous and less self-resilient than low self-critical students. They expressed self-critical thoughts with greater contempt, displayed significantly more insults and accepted critic more submissively. Additionally, they experienced more sadness and shame in response to the critic. Moreover, the self-critical individuals had problems to disengage themselves from their internal critic and to express more adaptive emotional reactions in response to it such as being angry, assertive or confident. This study added to the understanding of self-criticism that not just the content of criticism is internalized in self-critical individuals, but also its emotional tone of contempt and disgust, which reflects a deep emotional vulnerability of the self in response to the criticism. The authors conclude that trait self-criticism not only encompasses the tendency to be critical and perfectionistically demanding of oneself, but also an inability to withstand this self-assault. Hence, if core self-critical beliefs are emotionally-anchored, working with emotions needs to be a central aspect of challenging self-criticism in psychotherapy (Whelton & Greenberg, 2005).

As illustrated before, self-criticism is a commonly reported symptom in depressed patients and a direct target in psychotherapy for depression. Based on the assumption that cognitive and emotional schema pattern underlie harsh self-criticism, we used self-critical material as a trigger to study cognitive and emotional neural responses using fMRI. This approach might be a valid task for

studying alterations in the neural emotional and cognitive responding of depressed patients. If self-criticism proves to be a valid trigger for emotional and cognitive responses, this might allow for studying differences in the cognitive-emotional networks of acutely depressed patients compared to healthy controls including bottom-up and top-down information processing.

1.4 The Role of emotion in psychotherapy for depression

Cognitive therapy traditionally conceptualizes negative emotions as clinical symptoms that need to be reduced or contained. Moreover, changing specific depressogenic thoughts, beliefs, and attributions is expected to be sufficient for changing emotions (Beck et al., 1979). Indeed, changing cognitions within psychotherapy seems to have a great impact on symptom reduction in depressed patients (Butler et al., 2006; Dobson, 1989; Hofmann et al., 2012; Jakobsen et al., 2012). However, there might also be limitations in activating change by merely challenging cognitions. Greenberg (2004) argued that simple cognitive change is unlikely to reconfigure the underlying emotional networks. In his view, a top-down approach generally promotes problem-focused coping and might have the power to inhibit unpleasant emotions but bottom-up processing is essential for changing automatic emotional responding. Gilbert and colleagues (2006) claimed that some patients might be able to understand the logic of cognitive therapy and to generate alternative beliefs/thoughts, but they might not feel reassured by these interventions. This difficulty is probably familiar to practicing clinicians, in case patients believe something intellectually but not emotionally. It is now generally held that there is a distinction between intellectual and emotional modes of processing, both being highly integrated in cognitive-affective structures (e.g., Beevers, 2005; Greenberg, 2004; Greenberg & Safran, 1984; Teasdale, 1993). Hence, psychological interventions must target both cortical and subcortical levels (Greenberg, 2004; Samoilov & Goldfried, 2000). Whereas contemporary CBT addresses emotional aspects by particularly strengthening frontal control processes in order to enhance top-down control of subcortical reactions, the exact mechanisms of emotional processes in therapy sessions such as by exploring emotional networks via increasing in-session emotional arousal within CBT is still a neglected and largely under-researched issue.

There are a few studies pointing to the importance of emotional processes in cognitive therapy by showing a positive relationship between clients' in-session emotional experiencing and the reduction of depressive symptoms by the end of therapy (Auszra, Greenberg, & Herrmann, 2013; Castonguay et al., 1996; Grosse Holtforth et al., 2012). In addition, processes and techniques

related to emotional exploration and experiencing have been found to be positively linked with outcome across CBT and interpersonal therapy for depression (Coombs, Coleman, & Jones, 2002). Hunt and colleagues (2007) demonstrated the incremental effect of adding interventions fostering emotional processing to cognitive restructuring in a study examining depressive responses of at-risk subjects to the death, injury, or illness of a pet. In their study, subjects, who participated in a treatment combining cognitive restructuring with fostering emotional processing, showed greater recovery from depressive symptoms one month after treatment than subjects who received cognitive restructuring interventions alone. These findings suggest that adding emotion-focused interventions to cognitive interventions might improve outcomes in psychotherapy for depression. Emotion-Focused Therapy (EFT) for Depression (Greenberg & Watson, 2006) provides interventions (e.g., systematic evocative unfolding, focusing, two chair dialogue, and empty chair dialogue) that can be regarded as exposure interventions, in which the therapist activates schematic representations of dreaded experiences that are associated with intense emotions. Chapter 1.5.2 will provide more information about emotion-focused interventions in psychotherapy for depression.

Based on this theoretical background a clinical randomized-controlled trial was conducted in order to enhance knowledge about the role of emotional processing in the framework of CBT by deliberately fostering emotional processing by integrating interventions of EFT as well as Mindfulness-Based interventions to standard CBT. Teaching mindfulness skills (Segal, Williams, & Teasdale, 2002) helps patients to become aware of negative cognitions and emotions without becoming consumed by them or having to avoid them. From there, this approach may also be employed to facilitate exposure interventions.

1.5 A clinical randomized-controlled trial of psychotherapy for depression

This section provides a short summary of the design of the randomized-controlled trial (RCT) that builds the basis for all three studies presented in this thesis.

1.5.1 RCT design

The RCT was conducted to evaluate the effectiveness of a novel, theory-based depression treatment, i.e., Exposure-Based Cognitive Therapy (EBCT; Hayes et al., 2005). EBCT has specifically

been developed to accomplish more sustainable symptom relief by integrating principles of anxiety therapy (i.e., exposure), as well as EFT (i.e., emotional processing) and principles of mindfulness. In the current RCT, outcome and process variables of an adapted form of EBCT, EBCT-revised (EBCT-R) were studied in comparison with standard Cognitive Behavioral Therapy which is considered as the gold standard of psychotherapy with depressed patients (CBT; Hautzinger, 2003). After a broad screening process, suitable patients were randomized to one of two therapy conditions. Each patient received an individual therapy of 22 sessions as well as three follow-up booster sessions after 3, 6, and 12 months accompanied by a systematic assessment of outcome and process variables. In a subgroup of patients fulfilling inclusion criteria for fMRI, an fMRI session was applied before starting the treatment (**Figure 1**). For more information about screening and randomization procedures please consult manuscript I in chapter 2. Among other research questions, the applied design specifically allowed to study short- and long-term efficacy of both therapy conditions as well as cognitive and emotional mechanisms of change in psychotherapy for depression.

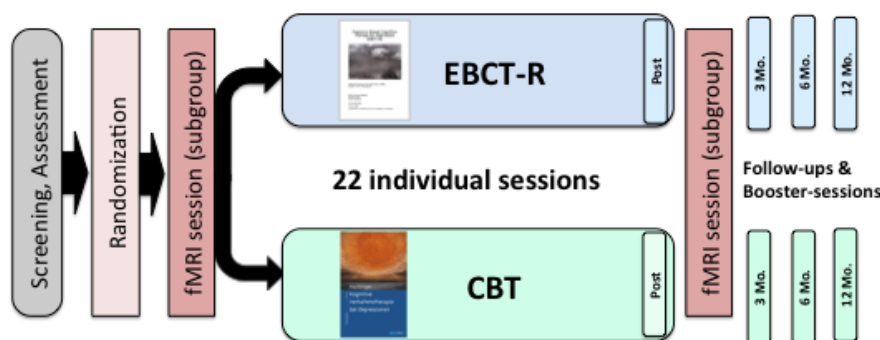


Figure 1 RCT design. fMRI = functional magnetic resonance imaging. EBCT-R = Exposure-Based Cognitive Therapy-revised. CBT = Cognitive Behavioral Therapy.

Study therapists were trained in CBT and EBCT-R and, to control for therapist effects, provided therapies in both conditions. Throughout treatment of all 22+3 sessions, therapists had to follow the respective treatment manual of CBT and EBCT-R, both consisting of three phases. The manuals were largely identical for the first and the third phases but differed substantially regarding specific techniques and process strategies during the second phase of therapy. The following two chapters will describe the treatments, underlying theories, and techniques of challenging self-critical thinking in more detail.

1.5.2 Exposure-Based Cognitive Therapy-revised

The three phases of EBCT-R included: strengthening, exposure/emotional processing, and consolidation. **Figure 2** gives an overview of phases and goals of the EBCT-R therapy. The core component of EBCT-R was the second phase integrating strategies of emotion-focused interventions from EFT (i.e., unfolding, focusing, two chair dialogue, and empty chair dialogue) to optimize emotional processing.




	Phase	Strategies	Number of Sess.
	1) Resource activation	<ul style="list-style-type: none"> • Alliance building, goal formulation • Activity scheduling • Mindfulness 	8
	2) Exposure & emotional processing	<ul style="list-style-type: none"> • Preventing experiential avoidance • Fostering emotional processing • Questioning negative self-referential cognitions 	9
	3) Consolidation	<ul style="list-style-type: none"> • Goal revision • Maintaining balanced self-image • Crisis management, relapse prevention 	5

Figure 2 The three phases of EBCT-R and approximate number of sessions of each phase.

EFT is an empirically supported approach that integrates client-centered and gestalt therapies. In this approach emotion is seen as centrally important in the construction of the self, the general functioning, and therapeutic change. In contrast to the cognitive model of depression, emotions and not cognitions are the targets and agents of change. Change is achieved by the empirically supported principles of awareness and arousal of emotions, enhancement of emotion regulation, reflection on emotion, and transformation of emotional schemas through activation of adaptive emotional experience. EFT works on the basic principle that people must first “arrive at a place before they can leave it.” Thus, an important goal of EFT is to activate distressing affective experience of a maladaptive emotion (e.g., fear of shame) to live and viscerally experience it. Arousal appears to be essential for therapeutic progress (Greenberg & Watson, 2006). However, empirical research converges on the notion that the combination of emotional arousal and the cognitive reflection of its meaning, rather than the mere activation of emotion, lead to lasting changes (Greenberg & Watson, 2006; Samoilov & Goldfried, 2000). Transformation then comes

from the patient accessing a new adaptive emotional state in the session.

The main intervention used to treat self-criticism within the EFT model is the two-chair dialogue exercise. Defining features of EFT are that interventions are marker-guided and process-directive. Thus, for example, when a marker for harsh self-criticism emerges during a session, two-chair work is indicated. Typical markers might be verbal statements of harsh self-criticism in the course of a session such as “I am a failure” or “I am too stupid” or “I am worthless”. In the framework of EFT, self-criticism is conceptualized as a conflict split between two aspects of the self. One part of the self, (usually referred to as the “inner critic”) severely criticizes and evaluates and thereby blocks the experiences and healthy needs of another, more submissive part of the self usually labeled as the “experiencing self”. In a two-chair intervention, the patient is encouraged to express one aspect (the “inner critic”) on one chair and the other (the “experiencing self”) while sitting in the other chair, switching as needed from one chair to the other as directed by the therapist. In this dialogue, thoughts, feelings, and needs of each part of the self are explored and communicated. The therapist’s role is to structure and coach the dialogue and to guide the process to a resolution of the split, which often is accompanied by a softening of the “inner critic” into a more compassionate stance. This negotiation of the two sides for integration might lead to enhanced self-acceptance, better self-esteem, and to build stronger emotional assertiveness or resilience against the harsh self-treatment of the “inner critic” (Greenberg & Watson, 2006). A recent pilot investigation of emotion-focused two-chair dialogue among self-critical clients has found this intervention associated with significant reductions in self-criticism, depressive and anxiety-related symptoms, and significant increases in self-compassion and self-reassurance after treatment and six months thereafter (Shahar et al., 2012). These results support the assumption that emotional processing is efficient in facilitating change.

1.5.3 Cognitive-Behavioral Therapy

In favor of a better comparability between the two therapies, we assigned the interventions in the CBT manual to three phases in order to achieve a similar structure as in EBCT-R with interventions fostering cognitive processing as opposed to emotional processing in the middle phase. The phases of CBT included: strengthening, cognitive interventions, and consolidation. **Figure 3** gives an overview of phases and goals of the CBT therapy. During the second phase of CBT, therapists were encouraged to help the patient identify and challenge dysfunctional automatic thoughts and to

restructure the patient's set of cognitions that formerly led to depressive affect via rational discussion and behavioral experiments. The crucial difference between the EBCT-R and the CBT manuals is that the CBT manual prohibits the use of any specific technique for increasing emotional arousal or preventing emotional avoidance in the second phase, but rather encourages therapists to focus on cognitive processes by following standard cognitive therapy procedures.




	Phase	Strategies	Number of Sess.
	1) Resource activation	<ul style="list-style-type: none"> • Goal formulation and relationship building • Cognitive therapy rationale • Activity scheduling 	8
	2) Cognitive interventions	<ul style="list-style-type: none"> • Identifying dysfunctional cognitions • Questioning dysfunctional cognitions and schemas • Establishing and training functional cognitions 	9
	3) Consolidation	<ul style="list-style-type: none"> • Assertiveness training and problem solving • Relapse prevention 	5

Figure 3 The three phases of CBT and approximate number of sessions of each phase.

The model underlying Cognitive Therapy (CT) and CBT, formulated by Aaron Beck (1979), holds that most of our emotions and behaviors are the result of what we think or believe in. The cognitive model states that in depression the processing of external events or internal stimuli is biased by underlying dysfunctional beliefs that are incorporated into relatively enduring cognitive structures (schemas). Stable dysfunctional beliefs might constitute a vulnerability to depression and lead to a variety of cognitive errors or biases that are not helpful and therefore maladaptive. When these schemas are activated, they tend to bias the information processing. Depressed individuals often experience negative “automatic thoughts” that are repetitive, persistent, and hardly controllable. The negative cognitive triad of depression (Beck, 1967) represents three types of negative thoughts often present in depressive states: Negative representations of the self (i.e., the self is worthless), the personal world (i.e., the world is unfair), and the future (i.e., the future is hopeless), and often acts as a resistant barrier to change.

CT and related interventions aim at fostering cognitive processing in order to change maladaptive or self-critical thoughts to more efficient, adaptive and rational beliefs having a positive impact on patient's emotional, cognitive, and behavioral responses. Two commonly used interventions to challenge self-criticism by modifying maladaptive thinking are cognitive restructuring and reattribution (Beck et al., 1979). Cognitive restructuring helps the patient to become more aware of thoughts in general and to learn to identify and dispute irrational or maladaptive thoughts. Reattribution techniques are used when patients tend to blame themselves for unpleasant and uncontrollable events. Patients then learn to assign the appropriate amount of responsibility to the self, but also to consider external factors that may have contributed to the adverse outcomes.

In summary, whilst emotions in CBT were considered consequences and correlates of cognitive processes, in EBCT-R emotions were considered central targets and agents of change. However, both theories share a sense that self-criticism becomes automated and needs to be activated before it can be fully recognized and fought by patients. This aim is attained through the application of cognitive and emotion-focused interventions, respectively. Notably, acknowledging the positive side of self-criticism, both interventions do not aim at completely eliminating self-criticism, but rather keeping healthier and more adaptive forms of it (Kannan & Levitt, 2013).

1.6 Neural correlates of depressive states and self-criticism

1.6.1 Altered brain circuits in depression

A wide range of brain networks associated with emotional and cognitive functioning might be implicated in the pathophysiology of depression. The three leading neurobiological models of MDD include the limbic-cortical, the cortical-striatal and the default mode network (Graham et al., 2013). Regarding altered emotional processing of emotional stimuli in depressed patients, there is considerable evidence for increased activation in subcortical, for example the striatum, and limbic areas (e.g., hippocampus, amygdala), especially in the amygdala as an important limbic node (e.g., DeRubeis, Siegle, & Hollon, 2008; Fu et al., 2004; Hooley et al., 2009; Kessler et al., 2011; Siegle et al., 2002). Interestingly, several studies even reported enhanced amygdala activity in depressed patients to masked emotional stimuli, possibly reflecting response to emotionally "implicit" and unconscious stimuli (e.g., Morris, Öhman, & Dolan, 1998; Sheline et al., 2001; Suslow et al., 2010). In addition, the ability to regulate experienced negative emotions might underlie an inhibitory top-

down pathway including several frontal brain structures that might in concert exert regulatory effects on limbic and subcortical brain structures (Johnstone et al., 2007; Ochsner et al., 2002; Phan et al., 2005). There is converging evidence for altered brain activity in this limbic-cortical circuit in acutely depressed patients (DeRubeis, Siegle, & Hollon, 2008) and depression-prone individuals (Hooley et al., 2009; Hooley, Siegle, & Gruber, 2012). **Figure 4** shows the location in the human brain of important brain structures altered during depressive states.

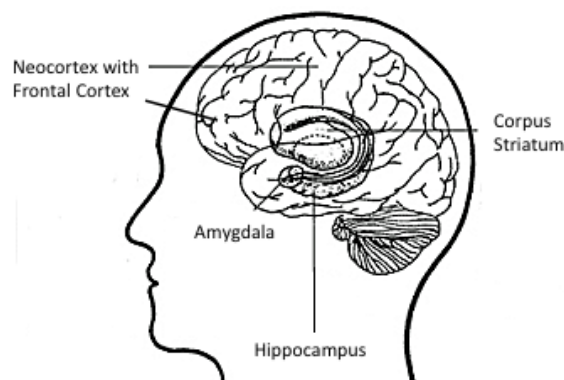


Figure 4 Location of important brain structures involved in depression
(adapted from: [http://mybrainnotes.com /memory-brain-stress.html](http://mybrainnotes.com/memory-brain-stress.html)).

1.6.2 Neural correlates of self-criticism

To date, a number of recent studies investigated the neural network involved in self-referential processing, highlighting the prominent role of the cortical midline structures and the default mode network in the processing of self-relevant information (see Qin & Northoff, 2011 for an overview). However, there are only a few studies that aim at examining brain response associated with self-criticism. Longe and colleagues (2010) investigated the neural correlates of self-criticism and self-reassurance in a healthy sample. Self-criticism was associated with neural activity in regions of the lateral prefrontal cortex and the dorsal anterior cingulate cortex, therefore linking self-critical thinking to error processing, error resolution and behavioral inhibition. In addition, activity in the dorsolateral prefrontal cortex was positively associated with high levels of self-reported self-criticism. Self-reassurance was associated with activity in regions that are also involved in the expression of compassion and empathy towards others, namely the left temporal pole and the

insular cortex. The authors concluded that the process of self-criticism might underlie a strong externalized focus and exclusively rely on top-down neural processing. Another possible explanation for this mainly frontal shaped neural activation pattern might also be the use of standardized stimulus material which might not have been sufficient to provoke emotions associated with personally significant self-critical aspects. In a recent study, Hooley and colleagues (2012) studied the impact of high self-critical thinking in a group including depressed, recovered depressed, and healthy participants. During the fMRI measurements, participants had to listen to tape-recorded critical utterances by their own mothers. Compared to participants with low self-criticism, those who scored high on self-criticism showed altered activation in a network of regions associated with emotion reactivity, including increased amygdala activity and decreased responses in prefrontal regulatory regions. In another study, using the same fMRI paradigm, remitted depressed patients failed to activate the dorsolateral prefrontal cortex and the anterior cingulate cortex and showed enhanced activity in the amygdala, while listening to the tapes as compared to healthy control participants (Hooley et al., 2009; Hooley et al., 2005). The authors conclude that criticism might be a risk factor for depression relapse because it activates the amygdala that seems to be a part of an altered cortical-limbic system underlying vulnerability to depression.

In summary, harsh self-criticism might trigger cognitive and affective responses underlying a broad cortical-subcortical brain system.

1.7 An integrative neurophysiological-psychological approach

A better understanding of treatment mechanisms and identification of reliable predictors of treatment response would constitute major progress in the fight against depression. The aim of the present thesis was to gain a more comprehensive understanding of the role of emotional processing in depressed patients from a psychological as well as from a neurophysiological point of view. The current work has several goals.

In a first step, we studied emotional processing as a process variable in the course of psychotherapy for depression and its relation to therapy outcome.

On a neural level, intense individualized self-criticism has been shown to be an important target in psychotherapy for depression that triggers emotional and cognitive responses. Thus, in a second step, we used self-criticism to study the neurophysiological correlates of the cognitive and

emotional components of information processing using fMRI in acutely depressed patients and healthy control participants.

The identification of neural predictors of therapy response using fMRI has shown promising results. In a further step we therefore investigated relationships between neural responses to self-criticism as an emotional stimulus and therapy response in acutely depressed patients prior to starting CBT.

The last goal is to advance our knowledge concerning psychological and neurobiological mechanisms that might explain the link between the neural correlates of emotional processing and the extent to which an individual might profit from the psychological treatment. Hence, we combined neurophysiological findings obtained with self-report process and outcome questionnaires.

Successful translation of research findings into clinical practice depends crucially on research that integrates standardized testing methods across multiple testing modalities (Kemp et al., 2008). The use of an integrative neurophysiological-psychological approach by combining fMRI findings with psychological outcome and process variables over time under an overarching theoretical framework might allow for a broader perspective of the interaction between cognitive, emotional, and biological factors in order to affect outcome and course of psychotherapy for depression. Moreover, the identification of neurobiological markers of successful therapy response might allow for a selection of more suitable treatments at an individual level.

Taken together, the present thesis integrates (1) the study of self-reported emotional processing in the context of a randomized-controlled trial of psychotherapy for depression (manuscript I), with (2) the investigation of neural correlates of cognitive and emotional processes of harsh self-criticism in healthy subjects (manuscript II), with (3) the study of altered neural responses to self-criticism in depressed patients as well as with the investigation of (4) brain activity in response to emotional stimuli as potential predictors of treatment response (manuscript III).

1.8 References

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2. Manuscripts

Exposure-Based Cognitive Therapy as an Intervention to Foster Emotional Processing in Depression: A Randomized Comparison with Cognitive-Behavioral Therapy

Martin Grosse Holtforth,^{1,2} Tobias Krieger,¹ David Altenstein,¹ Nadja Doerig,¹ Laurence Meisch,¹ and Adele M. Hayes³

¹Research Section Psychotherapy for Depression, Department of Psychology, University of Zurich, Switzerland.

²Division of Clinical Psychology and Psychotherapy, Department of Psychology, University of Bern, Switzerland.

³Department of Psychology, University of Delaware, USA.

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Abstract

Objective: Emotional processing is hypothesized to be a key mechanism of change across psychotherapy approaches. Exposure-based cognitive therapy for depression (EBCT; Hayes, et al., 2005/2007) is specifically designed to facilitate emotional processing by applying principles of exposure and affective arousal within a cognitive-behavioral therapy (CBT) framework. This is the first study to compare outcomes and the process of change in EBCT and CBT in a randomized clinical trial. The additional goals of this study were to examine whether: 1) EBCT was associated with a period of transient affective arousal, 2) emotional processing during this period predicted subsequent improvement in depression, and 3) whether this pattern of findings was specific to EBCT. **Method:** One hundred and forty-four depressed outpatients (56% female, mean age = 41, 100% Caucasian) were randomized to manualized EBCT (N = 73) or CBT (N = 71). Primary outcome was a self- (Beck Depression Inventory [BDI]) and a clinician-rated measure [Inventory of Depressive Symptomatology - Clinician Rated [IDS-C]) of depressive symptoms. Emotional processing was assessed by patient report after each therapy session. **Results:** Patients in both treatments improved significantly in measures of depressive symptoms, with large effect sizes (ESs: -1.68 – -1.87), and did not differ significantly on any measures of depression (ESs: -.17 – -.24). The pattern of symptom change in EBCT was cubic, suggesting a period of disturbance, and more emotional processing during this period predicted improvement in depression ($p = .03$). These findings were specific to EBCT. **Conclusions:** The findings suggest that EBCT might have its effects, as theorized, by facilitating affective engagement and emotional processing and that it might be as effective as gold standard CBT for depression.

Keywords: depression, cognitive-behavioral therapy, exposure-based cognitive therapy, exposure, emotional processing, mechanisms of change

Introduction

Emotional processing (EP) is hypothesized to be a central mechanism of change across psychotherapeutic approaches, and exposure-based and other affectively charged interventions are potent ways to facilitate EP (Foa & Kozak, 1986; Greenberg & Watson, 2006; Pascual-Leone & Greenberg, 2007). The term EP was originally introduced in the context of treatments for anxiety disorders and can generally be understood as changing maladaptive associations between stimuli, cognitive-emotional responses, and meaning. Other terms that have been used to describe this combination of increasing understanding and tolerance of emotions and coming to new meanings include cognitive-emotional processing (Rachman, 1980) and experiencing (Greenberg, Rice, & Elliott, 1996). Reviewing the available evidence on emotional processes that are most closely related to outcome, Greenberg and Pascual-Leone (2006) define EP by four central components: (1) awareness and arousal of emotion, (2) enhancement of emotion regulation, (3) reflection on emotion, and (4) transformation of emotion through activation of adaptive emotional experience. Empirical research seems to converge on the notion that the combination of emotional arousal and the cognitive reflection of its meaning, rather than the mere activation of emotion, is associated with lasting changes (Samoilov & Goldfried, 2000; Whelton, 2004). In support of the relevance of EP in depression change, Hunt and colleagues (Hunt, Schloss, Moonat, Poulos, & Wieland, 2007) showed that individuals who engaged in an EP exercise after a depressive event felt better in the long run than individuals who applied other strategies (i.e., cognitive restructuring, problem-solving or avoiding). In addition, EP has been reported to predict therapeutic change in experiential therapy (e.g., Pascual-Leone, 2009) and in dialectical behavior group therapy for depression (Feldman, Harley, Kerrigan, Jacobo, & Fava, 2009).

This understanding of EP corresponds with Carey's (2011) view of exposure as a fundamental component of successful interventions across theoretical orientations that essentially involves activating the relevant maladaptive pattern/network, challenging inconsistencies through corrective information, focusing the patient's attention on these inconsistencies, and facilitating new cognitive-emotional-behavioral responses. Rachman and Teasdale (1969) hypothesized that the principles of exposure and EP might also apply to the treatment of depression. Whereas there is substantial support for the efficacy of exposure-based interventions in the treatment of anxiety disorders (e.g., Richard & Lauterbach, 2011), the application of exposure

principles to the treatment of depression is rather novel (Hayes, Beevers, Feldman, Laurenceau, & Perlman, 2005; Neudeck & Wittchen, 2012; Wilamowska et al., 2010). Although exposure can serve as an overarching principle for treating anxiety and depression, the treatments might facilitate EP in somewhat different ways. Exposure in depression may involve decreasing avoidance and rumination and targeting the fear of negative and positive emotions, as well as fear of the negative views of self that are activated when depressed (Hayes, et al., 2005; Hayes et al., 2007). With a reduction in fear, the negative self-schema can be dislodged and opened to new information. In contrast, exposure in the treatment of anxiety disorders might focus more on distress tolerance, mobilizing habituation and extinction processes, as well as inhibition learning (Abramowitz, 2013; Craske et al., 2008).

Avoidance has played a central role in anxiety research (Clum & Knowles, 1991; Newman & Llera, 2011), but its relevance for the etiology and treatment of depression has received comparably little attention. In depression, maladaptive cognitive, emotional, and behavioral networks are assumed to contribute to a self-perpetuating cycle involving negative schematic mental models, ruminative thought patterns (Teasdale, 1999), and avoidant coping (Trew, 2011), all of which are strengthened with repeated depressive episodes and may be weakened by psychotherapeutic interventions (Beevers, Wells, & Miller, 2007). Consequently, avoidance has been proposed as an important risk factor for depression and a promising target of treatment (Hayes, et al., 2005; Ottenbreit & Dobson, 2008; Trew, 2011).

The general idea behind the fostering of EP when treating depression is that the therapist helps the patient to (a) decrease avoidance and ruminative patterns that maintain depression, (b) decrease the fear of negative and positive emotions, (c) explore and disrupt depressive patterns, and (d) develop new, more adaptive patterns. As a result, the patient learns to uncouple negative emotions and cognitions and to develop more adaptive associations between stimuli, responses, and meaning. EP is assumed to involve substantial and enduring changes of the mental representations that constitute a latent vulnerability for the development of depressive symptoms (Beevers, 2005; Teasdale, 1993), and thereby also to help prevent relapse (Hayes, et al., 2005; Hunt, et al., 2007).

In developing Exposure-Based Cognitive Therapy for depression (EBCT), Hayes and colleagues (Hayes, et al., 2005; Hayes, Feldman, et al., 2007) systematically applied the principles of exposure and EP (Foa & Kozak, 1986), as well as principles from emotion-focused therapy (Greenberg & Watson, 2006), and schema-focused therapies (Young, Klosko, & Weishaar, 2003).

EBCT includes three phases: The first phase focuses on teaching skills to reduce avoidance and rumination and increase engagement with emotions. The second phase involves gradual exposure to and processing of avoided emotions related to core feelings of defectiveness, failure, and worthlessness that includes considering corrective information, and coming to a new perspective and shift in affective responding. The final phase focuses on facilitating new, more adaptive patterns of functioning that can increase resilience and promote mental health after the depressive episode. The second phase is conceptualized as the exposure phase of therapy because it involves working through feared emotions and directly accessing and exploring negative experiences mindfully. EBCT is hypothesized to be associated with a transient increase in affective arousal, marked by a transient worsening of depressive symptoms, as patients approach disturbing material without engaging in previous patterns of avoidance and rumination. With repetition, the previously disturbing material becomes less feared and overwhelming, thereby allowing for EP and movement toward active problem solving, and a more balanced view of the self and one's future. The expectation of a transient worsening of mood in the middle phase of therapy also translates into a specific change pattern of symptom change. Although the shape of symptom change in successful psychotherapy is commonly described as continuous improvement, nonlinear patterns can also characterize the process of therapeutic change (Hayes, Laurenceau, Feldman, Strauss, & Cardaciotto, 2007). EBCT is hypothesized to be associated with a linear decrease in depressive symptoms in the early phase of treatment and then with a curvilinear pattern as affective arousal spikes over the second and third phases of treatment. Over the course of treatment, this would appear as a cubic trajectory (initial decrease in depression and then a transient symptom increase and decrease in affective engagement during the exposure phase).

In the first open trial of EBCT (Hayes, et al., 2005) with 29 patients diagnosed with Major Depressive Disorder (MDD), the treatment showed large effect sizes in reducing depressive symptoms. As predicted, growth curve analyses showed a cubic trajectory of symptom change. Peak levels of affective arousal and observer-rated EP occurred during the exposure phase, and the peak levels of EP predicted later symptom improvement. Conversely, avoidance was associated with less processing and worse outcomes (Hayes, Laurenceau, et al., 2007). In another open trial in Switzerland, using different measures of core constructs (Grosse Holtforth et al., 2012) as well as an adapted version of EBCT in 24 patients with MDD, EBCT was again associated with large effect sizes regarding the reduction in depressive symptoms and with a reduction in avoidance. EP in the exposure phase of treatment predicted symptom

improvement, and the course of change was cubic. The findings of the two pilot trials on EBCT lend further support to the central role of EP in therapeutic change and suggest that exposure principles might be fruitfully applied to the treatment of depression.

The aims of the current study were to evaluate the efficacy of EBCT and investigate EP as a possible mechanism of change. We conducted a randomized-controlled trial comparing EBCT with Cognitive-Behavior Therapy (CBT). In this study, CBT and EBCT are assumed to differ in three ways: In CBT, emotions were considered consequences and correlates of cognitive processes, whereas in EBCT emotions were considered a central target as well as a tool of change. CBT therapists were instructed to use techniques fostering cognitive restructuring but explicitly refrain from using emotion-focused techniques. Second, to prepare patients to tolerate strong negative emotions in EBCT, patients were taught selected mindfulness skills in the first phase of treatment, and mindfulness techniques were not taught in CBT. EBCT also included education about the functions of positive and negative emotions and healthy lifestyle habits to increase their resources for change, which were components not included in CBT. Based on the above-reported literature, we hypothesized that: 1) decreases in depression symptoms and improvements in well-being in EBCT would be comparable to those in CBT; 2) the pattern of change in depression symptoms and well-being in EBCT would be cubic; 3) in EBCT patients would report more EP than in CBT, and 4) more EP in the exposure phase of EBCT would predict better outcomes. The CBT comparison group allowed for an examination of the specificity of the cubic pattern and the predictive utility of EP to EBCT.

Methods

Participants

The outpatient clinic of the university's psychology department served as the site for the study, and the treatment was offered as research, separate from routine care. Treatment was free of charge, and participants were not compensated financially. The patient flow chart is shown in **Figure 1**.

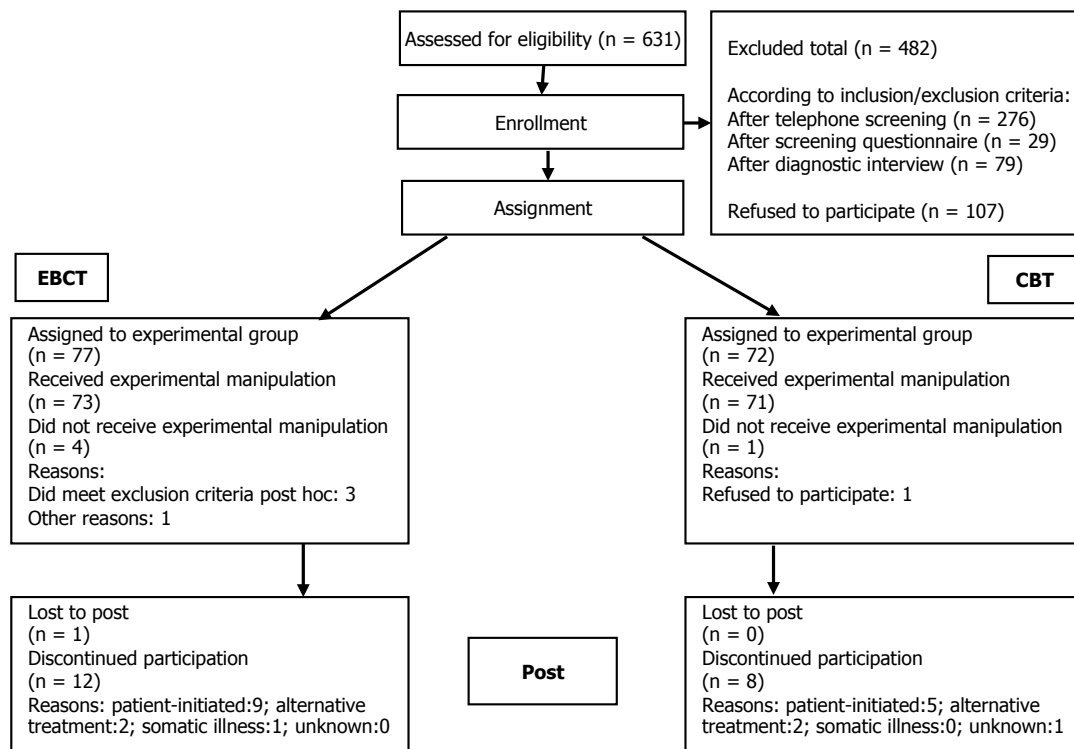


Figure 1 CONSORT flow chart. EBCT = Exposure Based Cognitive Therapy, CBT = Cognitive Behavioral Therapy.

A total of 631 individuals made an initial inquiry about the study and were assessed for eligibility. A-priori inclusion criteria were meeting Diagnostic and Statistical Manual of Mental Disorders (DSM–IV-TR; American Psychiatric Association, 2000) criteria for MDD, scoring at least 14 on the German version of the Beck Depression Inventory-II (BDI-II; Kühner, Bürger, Keller, & Hautzinger, 2007), and scoring no more than 13 points on the World Health Organization WHO-5 Well-Being Questionnaire (Henkel et al., 2004). Further inclusion criteria were being between the ages of 18 and 65 years, and giving informed consent to study participation. Exclusion criteria were meeting criteria for psychotic disorders (Schizophrenia, Schizophreniform, Schizoaffective, Psychosis NOS), Bipolar Disorder (current or lifetime), Borderline, Schizotypic or Antisocial Personality Disorder, current Substance Dependence, acute suicidality, or mood disorders due to medical conditions. Patients who took antidepressant medication at a stable dose for at least one month were allowed to participate.

Individuals meeting criteria for other comorbid disorders were also included, if patient, therapist, and the research team agreed that relief of depressive symptoms was the main

treatment goal and that the comorbid condition would not be the focus of interventions. Participants could not receive concurrent psychological treatments for depression, including individual or group psychotherapy. We also excluded individuals with health conditions that required medications potentially exacerbating depression (e.g., steroids). Excluded patients were informed about alternative therapeutic options in the community. A total of 482 of the 631 individuals screened were excluded by these criteria.

One hundred and forty-nine individuals were randomized after completing pre-treatment measures. Two patients did not start treatment after randomization. Additionally, early in treatment (i.e., session 1-3), three participants were excluded from the trial post randomization because they were found to meet exclusion criteria early in treatment (i.e., Borderline Personality Disorder or a past psychotic episode). **Table 1** gives an overview of the comparison of the 144 patients in the final intention-to-treat (ITT) sample. Patients did not significantly differ on any of the demographic or disorder-related variables.

Table 1 Patient characteristics at pre-treatment.

	EBCT (N = 73)	CBT (N = 71)	p-Value
Age in years (M[SD])	41.8 (11.6)	39.5 (11.1)	.23
	N (%)	N (%)	
Gender			.51
Female	39 (53.4)	42 (59.2)	
Male	34 (46.6)	29 (40.8)	
Marital status			.74
Single	28 (38.4)	30 (42.9)	
Married/in a relationship	31 (42.5)	25 (35.7)	
Separated/divorced/widowed	11 (15.1)	11 (15.7)	
Missing	3 (4.1)	4 (5.7)	
Education			.29
Less than 9 years	1 (1.4)	2 (2.9)	
Professional training	26 (35.6)	30 (42.9)	
Highschool	10 (13.7)	14 (20.0)	
University or higher	34 (46.6)	22 (31.4)	
Missing	2 (2.7)	2 (2.9)	
No. of previous depressive episodes			.06
0	24 (32.9)	18 (25.4)	
1	8 (11.0)	8 (11.3)	
2-5	22 (30.1)	14 (19.7)	
> 5	11 (15.1)	24 (33.8)	
Missing	8 (11.0)	7 (9.9)	
Length of Current Episode			.37
> 2 years	25 (34.2)	19 (27.1)	
< 2 years	47 (64.4)	51 (34.2)	
Missing	1 (1.4)	0 (0.0)	
Comorbid Anxiety Disorder			.86
Yes	24 (32.9)	25 (35.2)	
No	49 (67.1)	46 (64.8)	
Missing	0 (0.0)	0 (0.0)	
Comorbid Personality Disorder			.12
Yes	13 (17.8)	21 (29.6)	
No	60 (82.2)	50 (70.4)	
Missing	0 (0.0)	0 (0.0)	
Antidepressant Medication			.44
Yes	15 (20.5)	19 (26.8)	
No	58 (79.5)	52 (73.2)	
Missing	0 (0.0)	0 (0.0)	
Psychotherapy Experience			.49
Yes	40 (54.8)	41 (57.7)	
No	31 (42.5)	24 (33.8)	
Missing	2 (2.7)	6 (8.5)	

Note. EBCT = Exposure-Based Cognitive Therapy, CBT = Cognitive Behavioral Therapy.

Procedure

Patients were enrolled over a 26-month period from January 2010 to February 2012 and were recruited via local media, the internet, public advertisements, general practitioners, and local psychiatrists. After structured telephone screening and completion of screening questionnaires, eligible participants were invited for a diagnostic interview with a trained interviewer. All patients signed informed consent forms before the initial intake interview. An external researcher at a different university randomized therapy conditions (EBCT vs. CBT), and each therapist was assigned an equal number of cases in both conditions. All sessions were recorded on DVD with the patients' prior consent. The study protocol was approved by the responsible local ethics committee.

Power analysis, conducted with G*Power (Faul, Erdfelder, Lang, & Buchner, 2007), indicated that a between-group difference (two-tailed) with a large effect size ($d = .80$) with 80% power required a total sample size of $N = 52$, whereas a medium between-group effect size ($d = .50$) required a total sample size of $N = 128$. Therefore the present study's ITT sample size ($N = 144$) was sufficient to detect differences of moderate size between the groups.

Therapists, training and supervision

A total of 25 masters-level psychologists were recruited as therapists from local certified CBT training institutes. As part of their postgraduate training in psychotherapy, all therapists had received, among others, courses in cognitive-behavioral techniques and specifically of cognitive-behavioral therapy for depression. Therapists took part in a refresher training in CBT depression treatment, as well as an EBCT course containing emotion-focused techniques and selected mindfulness techniques. Twenty-two therapists were women and three were men; all were Caucasian. The therapists' average age was 31.4 years ($SD = 5.14$; 25-45). One therapist had completed her postgraduate therapy training, ten were in their third or fourth year of postgraduate training, and 14 were in their first or second year of postgraduate training. Each therapist treated on average 5.8 patients ($SD = 2.8$; 1-13) in the present study. To control for therapist effects (Baldwin & Imel, 2013), therapists were assigned equal numbers of patients in both conditions. During the trial, all therapists had condition-specific weekly DVD-based small-group supervision meetings. CBT supervisors were experienced therapists with at least 9 years of practical experience (three females, one male; age: 40-48 years). EBCT supervision was

conducted by one male and one female supervisor (age: 41/43 years) with seven and nine years of practical experience post training, respectively.

Treatments

Cognitive-Behavioral Therapy (CBT): The manualized CBT protocol was based on the cognitive therapy treatment for depression as outlined by Beck et al. (Beck, Rush, Shaw, & Emery, 1979). In the trial, the therapists used an adapted 22-session version of the well-established German-language manual by Hautzinger (2003). The adapted manual subdivided the treatment course into three phases to allow for a better comparison with the EBCT treatment (1. psychoeducation, individualized treatment rationale, and activity scheduling, 2. change of dysfunctional cognitions, and 3. assertiveness training, stabilization of gains, and relapse prevention).

Exposure-Based Cognitive Therapy (EBCT): The manualized EBCT (Grosse Holtforth, Sutter, & Schmied, 2009) was specifically designed to facilitate EP in a cognitive-behavioral therapy context. EBCT included three phases: 1) stress management skills, strengthening resources, scheduling rewarding activities, and identifying/interrupting patterns of avoidance and rumination, also including to gradually learn mindfulness meditation to increase distress tolerance and foster healthy engagement with emotions. The first phase prepared patients for the second phase of therapy, i.e., the EP/exposure phase. EP encompasses the experience, exploration, and better understanding of one's emotions. Using exercises that are akin to imaginal exposure, patients recall experiences related to their negative view of the self as defective, a failure, and/or as worthless. To foster EP, emotion-focused interventions, such as two-chair dialogue and empty chair dialogue (Greenberg & Watson, 2006), were employed. The third phase (consolidation and positive growth) included goal setting, developing a healthy view of self, clarifying their sense of meaning and purpose, addressing the fear of positive emotions and experiences, and relapse prevention. Length of treatment was constrained to 22 sessions and to be conducted weekly up to two thirds of the sessions.

For purposes of optimizing treatment adherence beyond manualization and DVD-based supervision, therapists also completed intervention checklists after each session. For post-hoc adherence checks, therapists completed session-report questionnaires after each session. One scale assessed the use of EBCT-specific interventions (e.g., "In today's session, I tried to involve

the patient emotionally”; $\alpha = .86$), whereas another scale assessed the use of CBT-specific interventions (e.g., “In today’s session, I worked toward an improvement of the patient’s skills to manage problematic situations”; $\alpha = .83$). According to mean scores for each therapy across all 22 sessions, therapists reported having used more EBCT-specific interventions in EBCT ($M = 3.58$, $SE = 0.69$) than in CBT ($M = 3.16$, $SE = 0.83$), $t[140] = 3.24$, $p = .001$, $d = .55$), and having used more CBT-specific interventions in CBT ($M = 3.28$, $SE = 0.75$) than in EBCT ($M = 2.96$, $SE = 0.75$), $t(140) = 2.50$, $p = .014$, $d = .42$). In addition, treatment adherence was assessed by blinded observer-ratings on the basis of DVD recordings of single sessions. The adherence scale for CBT was based on the Collaborative Study Psychotherapy Rating Scale (CSPRS; e.g., Hill, O’Grady, & Elkin, 1992). For EBCT specific items were generated from the manual. The instrument contained 21 items across two subscales: CBT-specific interventions (13 items; $\alpha = .76$); and EBCT specific interventions (eight items; $\alpha = .64$). One additional item asked the rater to guess the treatment condition the therapy was in. To assess interrater agreement, we calculated intraclass correlation coefficients (ICC; Shrout & Fleiss, 1979) between ratings obtained from 21 videos rated by both judges. The two subscales showed acceptable (ICC > .60; Shrout, Spitzer, & Fleiss, 1987) interrater agreement (ICCs: CBT = .78, EBCT = .66). Subsequently, one session was randomly selected from the middle phase of treatment (sessions 11-16) for each patient in the completer sample and was rated by the observers. *T*-tests confirmed that adherence to EBCT was significantly higher in EBCT ($M = 0.95$, $SD = 0.60$) than in CBT ($M = 0.30$, $SD = 0.26$), $t[119] = 7.72$, $p < .001$, $d = 1.42$), and CBT adherence was significantly higher in CBT ($M = 1.13$, $SD = 0.65$) than in EBCT ($M = 0.56$, $SD = 0.33$), $t[119] = 6.19$, $p < .001$, $d = 1.13$). Additionally, the blind raters categorized 84 % of the EBCT and 89 % of the CBT sessions correctly. Furthermore, after completing the trial, therapists retrospectively rated their allegiance using three items for each condition (e.g., “How effectively did EBCT/CBT treat the patients’ depression?”; EBCT: $\alpha = .75$; CBT: $\alpha = .83$). On average, therapists reported comparable levels of allegiance with EBCT and CBT (EBCT: $M = 5.00$, $SD = .82$; CBT: $M = 4.65$; $SD = .99$; $t[23] = 1.25$; $p = .20$, $d = .52$).

Measures

Primary outcome measures for the present study were the *Beck Depression Inventory-II* (BDI-II; Hautzinger, Keller, & Kühner, 2006), the *Inventory of Depressive Symptomatology - Clinician Rated* 30-item version (IDS-C; Rush, Carmody, & Reimnitz, 2000) and the Depression section of the *Structured Clinical Interview for the DSM-IV Axis I and II Disorders* (SCID; First, Spitzer,

Williams, & Gibbon, 1995; Wittchen, Fydrich, & Zaudig, 1997). The BDI-II was administered at intake (pre), at sessions 8 (end of phase 1) and 16 (end of phase 2) and at termination (post). The German BDI-II (Hautzinger, et al., 2006) has previously shown satisfactory internal consistency and test-retest reliability, good convergent and discriminant validity, as well as a good sensitivity to change (Kühner, et al., 2007). In the current sample, Cronbach's alpha was .87. Trained interviewers (research assistants or graduate students) conducted the diagnostic interviews before therapy assignment (face-to-face) as well as at termination (via telephone) including the SCID and the IDS-C. At termination only the depression section of the SCID was conducted. For our SCID-I interviews interrater agreement (based on a random selection of DVDs of 22 % of our interviews) was $\kappa = .65$ for MDD and $\kappa = .80$ for the course (single or recurrent episode) of the depression. The German IDS-C has shown very good psychometric properties in previous studies (e.g., Drieling, Schäfer, & Langosch, 2007).

We assessed the following secondary outcome measures: The German short version of the *Inventory of Interpersonal Problems-Circumplex Scale* (IIP-32; Thomas, Brähler, & Strauss, 2011) assesses interpersonal functioning. In the present sample, Cronbach's α of the IIP-32 total score was .83. In the *Dysfunctional Attitude Scale* (DAS; Hautzinger, Joormann, & Keller, 2005; Weissman & Beck, 1978), patients answered 40 Likert-scaled items. Cronbach's alpha for the total score in the present study was .92. The *Self-Compassion Scale* (SCS; Neff, 2003) is a 26-item self-report inventory the six subscales of which can be summarized in a total score that has shown good construct validity, high internal consistency, and retest reliability (Hupfeld & Ruffieux, 2011; Neff, 2003). Cronbach's alpha in the present study was .82. With the *Cognitive-Behavioral Avoidance Scales* (CBAS; Ottenbreit & Dobson, 2004; Röthlin et al., 2010), patients rated 31 items on how much they avoid in general. The German CBAS demonstrated good internal consistency and test-retest reliabilities, as well as specificity of avoidance to depression. Cronbach's alpha in the present study was .83 for the total score. The *Emotion-Regulation Skills Questionnaire* (ERSQ; Berking & Znoj, 2008) is a self-report questionnaire assessing self-reported emotional competency on a 5-point Likert-scale. The total score of the ERSQ has shown good psychometric properties in clinical and non-clinical samples (Berking & Znoj, 2008). Cronbach's α for the total score in the present study was .89.

For analyses of symptom course, we used the BDI-II and the *WHO-5 Well-Being Index* (WHO-5; World Health Organization, 1998). The BDI-II was administered four times across treatment and the WHO-5 before each session. The WHO-5 measures (lack of) positive mood, vitality, and

general interest and engagement and has been shown to be a promising measure in treatment course monitoring (Newnham, Hooke, & Page, 2010). Cronbach's alpha in the present study was .90.

Patient experiences were assessed by brief post-session questionnaires completed after each session. EP was assessed by a brief self-report questionnaire designed to capture its empirically-based components: emotional awareness/arousal, emotional regulation, active reflection on emotion (meaning making), and emotional transformation (Pascual-Leone & Greenberg, 2007). However, we decided not to include the emotional transformation item because it captures the end point of processing and is therefore better conceptualized as an outcome variable. The final version of the scale consisted of seven items that began with the stem "In today's session" (e.g., "I could accept painful feelings/experiences"; "It became clear to me how my feelings are triggered"). The patients noted their responses on a Likert scale from -3 (*not at all*) to +3 (*yes, exactly right*). The internal consistency was $\alpha = .73$.

Statistical Analyses

Group differences in demographic data and pre-treatment measures were analyzed with independent *t*-tests and χ^2 -tests. To test between-subject intervention effects from baseline to termination regarding primary and secondary outcome measures, we used mixed models (Fitzmaurice, Laird, & Ware, 2004) with repeated measures (level 1) nested within participants (level 2). Mixed models impose minimal restrictions on change over time and covariance among repeated measures. Moreover, they can handle incompleteness due to missing data, which is important in intention-to-treat (ITT) analyses. In order to test our first hypothesis that treatment groups differ on changes from baseline to termination, we tested a model including main effects of time (0 = baseline score; 1 = termination score) and treatment (-0.5 = EBCT; 0.5 = CBT), and the interaction of time and treatment as predictor variables with the primary or secondary measures as the outcome variable in the ITT-sample. Within-group and between-group effect sizes (ESs) were calculated based on recommendations for calculating ESs for mixed effect models in controlled trials by Feingold (2009). We do not report confidence intervals (CIs) for these ESs because there is no consensus regarding ESs in mixed models, which would necessarily preclude CIs for ESs (Odgaard & Fowler, 2010). In addition, two dichotomous variables, i.e., the absence of a SCID MDD diagnoses at termination and a 50% improvement from baseline to termination (PI-50; Hiller, Schindler, & Lambert, 2012), were compared

between the treatments in the completer sample using χ^2 -tests. The shape of change was examined using mixed models. For this, linear, quadratic, and cubic orthonormalized polynomial coefficients were used as time-based predictors (Hedeker, 2004). All mixed models were tested applying restricted maximum likelihood (REML) estimation. To test our last two hypotheses, mean EP scores were calculated for the first phase (sessions 1-7) and second phase (sessions 8-16) of therapy. Differences in patient-reported levels of EP were then investigated by means of independent (between treatments) or dependent (within a treatment) t -tests. Furthermore, individual phase-specific mean scores of EP were examined as predictors of BDI-II and WHO-5 scores at termination. Baseline depression (or well-being) scores were controlled for phase 1 analyses, and the first intermediate scores (at session 8) were controlled for phase 2 analyses.

Results

Patient characteristics of all patients randomized to the two treatments are presented in **Table 1**. They did not differ significantly between the two groups (all $ps > .06$). One hundred and twenty-four patients (EBCT: $n = 61$; CBT: $n = 63$) attended at least 14 sessions of psychotherapy ($M = 21.4$, $SD = 1.3$) and were classified as completers, whereas 20 were classified as dropouts (EBCT/CBT: $n = 12/8$). Treatments did not differ with regard to number of dropouts ($\chi^2[1] = .87$, $p = .35$) and there were no statistically significant differences between completers and dropouts on any measured patient characteristics (all $ps > .10$). Dropouts were either patient-initiated ($n = 9/5$), due to a commencement of alternative psychological treatments ($n = 2/2$), due to somatic illness ($n = 1/0$), or for reasons being unknown to the researchers ($n = 0/1$). The timing of the dropout (session number) did not differ between the two treatments (median: EBCT = session 7, CBT = session 6; range: 1-18; U -test: $p = .91$).

Overall treatment efficacy and clinical significance of change

Table 2 shows means and standard deviations of the completer sample for baseline and termination score and changes in primary and secondary outcome measures based on mixed models for the ITT sample. With regard to primary outcome measures, patients in EBCT and CBT showed highly significant improvements in depressive symptoms on the BDI-II and IDS-C from pre- to post-treatment (all $ps < .01$). However, interaction effects ($group \times time$) were non-significant, indicating that there was no significant outcome difference between EBCT and CBT.

Table 2 Descriptives of raw scores in the completer sample (a) and coefficients for mixed effects models with the intention-to-treat sample (b).

a)	EBCT (n=60)		CBT (n=63)	
	Pre	Post	Pre	Post
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
BDI-II	24.62 (8.50)	9.39 (7.78)	26.01 (9.40)	9.51 (8.69)
IDS-C	31.80 (8.56)	14.75 (9.68)	32.95 (10.73)	14.06 (8.36)
WHO-5	1.23 (0.81)	2.68 (1.14)	1.09 (0.75)	2.71 (1.13)
IIP-32	1.69 (.47)	1.52 (.51)	1.75 (.43)	1.63 (.49)
CBAS	2.79 (.55)	2.34 (.62)	2.91 (.62)	2.42 (.65)
ERSQ	3.02 (.45)	3.69 (.59)	3.02 (.53)	3.56 (.66)
SCS	2.58 (.48)	3.01 (.53)	2.56 (.54)	2.90 (.62)
DAS	121.16 (27.59)	110.27 (29.39)	127.07 (28.17)	113.51 (30.09)

b)	Time			Group			Time x Group		
	<i>B</i>	<i>SE</i>	<i>t</i>	<i>B</i>	<i>SE</i>	<i>t</i>	<i>B</i>	<i>SE</i>	<i>t</i>
BDI-II^a	-15.26	1.23	-12.40*	1.70	1.49	1.14	-1.49	1.73	-0.86
IDS-C	-16.68	1.54	-10.86*	1.66	1.65	1.00	-2.37	2.17	-1.09
WHO-5	1.42	0.15	9.54*	-0.24	0.14	-1.78	0.22	0.21	1.07
IIP-32	-0.17	0.05	-3.60*	0.04	0.08	0.47	0.05	0.07	0.77
CBAS	-0.45	0.08	-5.91*	0.15	0.10	1.48	-0.05	0.11	-0.47
ERSQ	0.67	0.08	8.27*	-0.00	0.09	-0.05	-0.12	0.11	-1.06
SCS	0.43	0.07	6.06*	0.00	0.09	0.05	-0.10	0.10	-0.98
DAS	-11.07	3.05	-3.63*	8.09	4.79	1.69	-3.31	4.27	-0.77

Note. EBCT = Exposure-Based Cognitive Therapy, CBT = Cognitive Behavioral Therapy, BDI = Beck Depression Inventory-II, IDS-C = Inventory of Depressive Symptoms - Clinician Rated, WHO-5 = Well-Being Index of the World Health Organization, IIP-32 = Inventory of Interpersonal Problems – 32 item version, CBAS = Cognitive-Behavioral Avoidance Scale, ERSQ = Emotion-Regulation Skills Questionnaire, SCS = Self-Compassion Scale, DAS = Dysfunctional Attitude Scale. ^a Mixed models for the BDI-II as well as all the other measures are based solely on pre and post assessments. * $p < .01$.

Furthermore, analyses showed that patients changed significantly on all secondary outcome measures from pre to post (all $ps < .01$), and there were no substantial differences between EBCT and CBT in change over time on any of the secondary measures. Within- and between ESs (Cohen's d) for all measures are displayed in **Table 3**.

Table 3 Within- and between-group effect sizes (Cohen's *d*) for the intention-to-treat sample based on the coefficients of mixed models.

	Within-group ES		Between-group ES
	EBCT	CBT	
BDI-II	-1.70	-1.87	-.17
IDS	-1.68	-1.92	-.24
WHO-5	1.75	2.02	.27
IIP	-.37	-.26	.11
CBAS	-.72	-.80	-.08
ERSQ	1.30	1.06	-.23
SCS	.82	.64	-.19
DAS	-.38	-.50	-.11

Note. ES = Effect size. EBCT = Exposure-Based Cognitive Therapy, CBT = Cognitive Behavioral Therapy, BDI-II = Beck Depression Inventory-II, IDS-C = Inventory of Depressive Symptoms – Clinician Rated, WHO-5 = Well-Being Index of the World Health Organization, IIP-32 = Inventory of Interpersonal Problems – 32 item version, CBAS = Cognitive-Behavioral Avoidance Scale, ERSQ = Emotion-Regulation Skills Questionnaire, SCS = Self-Compassion Scale, DAS = Dysfunctional Attitude Scale.

To examine clinical significance, we computed treatment response status based on two different dichotomous variables at termination: a) 50% improvement (PI-50) from baseline on the BDI-II, and b) MDD SCID diagnoses. Using these criteria, 43 of 60 (72%) of patients in the EBCT condition showed clinically significant responses to treatment, and 48 of 63 (76%) patients in the CBT condition did. This difference was not statistically significant ($\chi^2[1] = .33, p = .57$). In addition, 51 of 59 patients (86%) in EBCT no longer met the SCID criteria for a MDD, and the same percentage (54 of 63, 86%) in the CBT condition did not ($\chi^2[1] = 0.01, p = .91$).

Shape of change, treatment process, and process-outcome prediction

Results of the multilevel analyses of shape of change are presented in **Table 4**. Whereas for EBCT there was a significant cubic pattern (i.e., transient worsening of symptoms) on both measures, in CBT there was a significant quadratic pattern on both measures (early reduction in symptoms and subsequent leveling off). Within each treatment patients reported significantly more EP in phase 2 than in phase 1 (EBCT: $M(SD)_{ph1} = 3.47 (0.43)$, $M(SD)_{ph2} = 3.81 (0.45)$; $t(59) = 8.85, p < .01, d = 2.30$; CBT: $M(SD)_{ph1} = 3.63 (0.41)$, $M(SD)_{ph2} = 3.79 (0.46)$, $t[62] = 4.59, p < .01, d = 1.17$). With respect to between treatment differences, patients in CBT in phase 1 reported significantly more EP than in EBCT ($t[121] = 2.18, p < .05, d = .40$), and there was no difference in

patient-reported EP between the two treatments in phase 2 ($t[121] = 0.17, p = .86, d = .03$). In addition, more EP in phase 2 of EBCT predicted more improvement on the BDI-II ($B = -4.36, SE = 1.92, t = -2.27, p = .03$) and the WHO-5 ($B = -0.71, SE = 0.30, t = 2.40, p = .02$). Interestingly, these findings were specific for phase 2 and not phase 1 (EBCT: BDI-II_{ph1}: $B = -2.11, SE = 2.23, t = -0.94, p = .35$; WHO-5_{ph1}: $B = 0.26, SE = 0.35, t = 0.74, p = .46$) and were specific to EBCT and not to CBT (CBT: BDI-II_{ph1}: $B = -2.78, SE = 2.60, t = 1.07, p = .29$; BDI-II_{ph2}: $B = -1.08, SE = 2.14, t = -0.51, p = .61$; WHO-5_{ph1}: $B = 0.45, SE = 0.32, t = 1.38, p = .17$; WHO-5_{ph2}: $B = 0.49, SE = 0.30, t = 1.66, p = .10$).

Table 4 Parameter estimates for change in well-being (WHO-5) and the Beck Depression Inventory – II (BDI-II) over the course of treatment for the completer sample.

EBCT				CBT		
WHO-5 course ^a						
Fixed effect	Coefficient	SE	t	Coefficient	SE	t
Intercept	0.02	.10	0.24	-0.00	.10	-0.04
Linear	9.15	.65	13.97***	11.02	.66	16.80***
Quadratic	-1.32	.65	-2.02*	-2.05	.65	-3.13**
Cubic	1.67	.65	2.54*	0.96	.65	1.47
BDI-II course ^b						
Fixed effect	Coefficient	SE	t	Coefficient	SE	t
Intercept	15.65	0.80	19.47***	16.59	0.89	18.62***
Linear	-84.04	5.68	-14.80***	-93.53	6.19	-15.10***
Quadratic	20.88	5.70	3.67***	19.37	6.21	3.12**
Cubic	-11.50	5.68	-2.02*	-11.58	6.23	-1.85

Note. EBCT = Exposure-Based Cognitive Therapy, CBT = Cognitive Behavior Therapy, WHO-5 = Well-Being Index of the World Health Organization, BDI-II = Beck Depression Inventory – II. Parameters are based on normalized orthogonal polynomial coefficients.

^aThe WHO-5 was assessed before each session over the course of therapy. ^bThe BDI-II was assessed four times (at baseline [= 0], at session 8 [= 1], at session 16 [= 2], and at termination [= 3]) over the course of therapy. ** $p < .01$. * $p < .05$.

Discussion

We set out to examine the role of EP in two cognitive-behavioral psychotherapies for depression. In a randomized-controlled study, we compared CBT with EBCT, which explicitly tries to foster EP by employing emotion-focused and mindfulness-based interventions. EBCT was assumed to differ from CBT in the enhanced focus on emotions in the processing phase, as well as increasing patients' distress tolerance by teaching mindfulness skills, stress management, and healthy lifestyle habits. To maximize EP, EBCT employs exposure- and other emotion-focused techniques in the second phase of treatment, whereas CBT therapists were instructed to refrain from emotion-focused techniques and only use cognitive interventions for schema change. In addition, we expected that higher levels of EP in EBCT would predict better treatment outcomes. Furthermore, we hypothesized a cubic change pattern over time in EBCT and a quadratic pattern in CBT.

Results indicated that patients in both, EBCT and CBT showed significant improvements in depressive symptoms from pre to post treatment, and results did not differ significantly between groups. As in earlier pilot studies (Grosse Holtforth, et al., 2012; Hayes, Feldman, et al., 2007), this integration of cognitive-behavioral with emotion-focused and mindfulness-based interventions in EBCT worked very well in an outpatient setting, and there was a fairly low level of attrition, supporting the feasibility and acceptability of EBCT. Both EBCT and CBT yielded outcomes that are in line with benchmarks from previous controlled trials with depressed outpatients (Minami, Wampold, Serlin, Kircher, & Brown, 2007). However, differences between the treatments in ESs on secondary variables were only small and non-significant.

EBCT is based on the premise that exposure and emotion-focused interventions related to one's core negative self-schemata would increase affective engagement and facilitate EP, which is considered a key predictor of change (Hayes, et al., 2005; Hayes, Feldman, et al., 2007). As hypothesized, EBCT showed a cubic pattern of change in depression symptoms and well-being, which suggests a transient increase in affective engagement during the exposure phase of treatment. This replicates findings from two open trials of EBCT (Grosse Holtforth, et al., 2012; Hayes, et al., 2005) showing similar patterns of change. In contrast, CBT in the current study showed a quadratic pattern of change that was characterized by an early decrease in symptoms and less change after that. A particularly interesting set of findings was that EP in the exposure phase of EBCT predicted improvement in both depression (BDI-II) and well-being (WHO-5), and

this was specific to the exposure phase of treatment and specific to EBCT. Although levels of EP in EBCT and CBT did not differ significantly in this phase, this processing was a predictor of improvement in the EBCT treatment. Whereas in CBT, EP was higher in the first phase, processing again did not predict outcome in CBT.

The present results regarding similar outcomes are similar to those by Watson and colleagues (Watson, Gordon, Stermac, Kalogerakos, & Steckley, 2003), who compared EFT and CBT in an RCT. Whereas secondary analyses of these data with observer ratings revealed that EP was higher in EFT than in CBT (Watson & Bedard, 2006), in our study, analyzing patient reports of emotional-processing, we did not find the expected differences between EBCT and CBT. It is possible that observer ratings of processing might reveal differences that self-reports do not capture. In addition, the emotion-focused interventions within EBCT in the current study may not have sufficed to result in higher levels of emotional processing (Greenberg, 2012).

Whereas some EP is to be expected also in CBT (Carey, 2011), somewhat surprisingly in phase 1 of CBT, patients reported more EP than in EBCT. This finding might be explained by the therapists explicitly refraining from emotionally challenging work in the first phase of EBCT, whereas EP might have occurred more naturally as a by-product in the first phase of CBT. Notably, early EP in CBT did not predict treatment outcome. More importantly, our results show that EP in phase 2 predicted improvement in depressive symptoms and well-being in EBCT, but not in CBT. This specificity might be explained by EP occurring in different contexts in EBCT as compared to CBT. Whereas exposure and processing in EBCT is supposed to take place *within* the session, in CBT most of EP might take place *outside* of the therapy room, for example in homework activities such as behavioral tests of dysfunctional thoughts. Because in this trial EP outside of the sessions was not explicitly captured by the post session measure, EP assessed by this measure may have failed to predict outcome in CBT. However still unexplained remains the finding that EP was equally strong in both conditions. Most likely, absolute levels of self-reported EP in EBCT and in CBT do not adequately capture qualitative differences in EP between the conditions that may be better captured by observer-ratings. With regard to the shape of change in this study, the differential change patterns were identified, replicating the findings of our pilot study and also of the findings of Hayes et al.'s (2005) pilot study.

There are several potential limitations that could impede the discovery of change processes and outcome differences. First, the therapists' previous clinical experience was comparably low, and the EBCT training was rather short. It might be that the therapists were not sufficiently prepared

for the competent implementation of relatively new techniques. Second, we were able to examine the relative adherence to the different manuals using DVD-recordings of the middle phases of each therapy and therapists' self-reported adherence, but we do not have sufficient information about potential cross-over or carry-over effects over whole therapies or of adherence in the first and third phases of treatment. Third, the measure utilized to assess EP was used for the first time. Whereas the scale had sufficient content validity and reliability, this self-report measure has not been tested on a larger scale yet. Lastly, it is important to mention that with the current sample size, we were not able to detect small ESs and that present results can not be generalized to other ethnicities than Caucasians.

A next step in testing EP as a possible mechanism of change in depression treatment will be to analyze the differential sustainability of the therapy effects in EBCT and CBT. This includes the comparison of long-term outcomes of EBCT and CBT, as well as investigating the differential prediction of long-term outcomes by the level of EP in therapy. Furthermore, process observer-ratings to code therapy sessions may provide further insights into the microstructure of avoidance, EP, view of self, and their interrelations. In addition, future research may also capture both EP taking place inside and outside of the therapy room.

Clinical Implications

We have shown that the integrative EBCT for the treatment of acutely depressed patients could be feasibly implemented by rather inexperienced therapists and yielded excellent outcomes. The findings suggest that EBCT might have its effects, as theorized, by facilitating affective engagement and EP and that it might be as effective as gold standard CBT for depression. The results of the current trial are encouraging with regard to the usefulness of integrating interventions to target multiple risk factors of depression and relapse, as does EBCT. However it remains to be shown whether such psychotherapy integration has augmented prophylactic effects.

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Neural Representation and Clinically Relevant Moderators of Individualised Self-Criticism in Healthy Subjects

Nadja Doerig,^{1,2} Yolanda Schlumpf,^{1,2} Simona Spinelli,^{2,3,4} Jakub Späti,² Janis Brakowski,² Boris B. Quednow,^{2,3} Erich Seifritz,^{2,3,4} and Martin Grosse Holtforth¹

¹ Psychology Department, University of Zurich, Zurich, Switzerland.

² Neuroscience Center, University and ETH Zurich, Zurich, Switzerland.

³ Department of Psychiatry, Psychotherapy and Psychosomatics, Zurich University Hospital of Psychiatry, Zurich, Switzerland.

⁴ Zurich Center for Integrative Human Physiology, Zurich, Switzerland.

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Abstract

Many people routinely criticise themselves. While self-criticism is largely unproblematic for most individuals, depressed patients exhibit excessive self-critical thinking, which leads to strong negative affects. We used functional magnetic resonance imaging in healthy subjects ($N = 20$) to investigate neural correlates and possible psychological moderators of self-critical processing. Stimuli consisted of individually selected adjectives of personally negative content and were contrasted with neutral and negative non-self-referential adjectives. We found that confrontation with self-critical material yielded neural activity in regions involved in emotions (anterior insula/hippocampus–amygdala formation) and in anterior and posterior cortical midline structures, which are associated with self-referential and autobiographical memory processing. Furthermore, contrasts revealed an extended network of bilateral frontal brain areas. We suggest that the co-activation of superior and inferior lateral frontal brain regions reflects the recruitment of a frontal top–down pathway, representing cognitive reappraisal strategies for dealing with evoked negative affects. In addition, activation of right superior frontal areas was positively associated with neuroticism and negatively associated with cognitive reappraisal. Although these findings may not be specific to negative stimuli, they support a role for clinically relevant personality traits in successful regulation of emotion during confrontation with self-critical material.

Introduction

Human beings routinely compare themselves to internalised standards and normally strive to minimise the gap between differing representations of the self; these gaps are known as self-discrepancies. Disagreement between how people see themselves and how they want to be seen by others may cause emotional and psychological derangement (Higgins, 1987) that may surface as harsh self-criticism. Self-criticism is a form of negative self-judgment and self-evaluation, and it may concern various aspects of the self, such as physical appearance, social behaviour, inner thoughts and emotions, personality characteristics and intellectual abilities (Gilbert and Miles, 2000). The potentially harmful impact of self-criticism on mental health and its central involvement in depressive pathology (Blatt, 1982; Carver, 1983) raise the question of how healthy people deal with perceived self-discrepancies without experiencing adverse consequences.

Although a number of recent studies investigated the neural network involved in self-referential processing of healthy participants (see Qin and Northoff, 2011 for an overview) and depressed patients (Grimm et al., 2009; Johnson et al., 2009; Lemogne et al., 2012; Yoshimura et al., 2013), the neural correlates of harsh self-criticism are less understood. In a recent functional magnetic resonance imaging (fMRI) experiment, Longe et al. (2010) confronted healthy participants with various scenarios focusing on personal setbacks, mistakes or failures. Compared with neutral scenarios, self-critical processing was associated with activity in the lateral frontal cortex and the dorsal anterior cingulate cortex (ACC), suggesting possible associations between self-critical thinking, error processing and behavioural inhibition (Longe et al., 2010). In this experiment, participants were instructed to imagine being either self-critical or self-reassuring in standardised situation scenarios. In our study, we fostered self-relevance and emotional responses by presenting individually tailored self-critical stimuli. The processing self-critical stimuli can be conceptualised as an instance of self-referential processing which has been associated with activity in the default mode network in several independent studies (see van Buuren et al., 2010 for an overview). Within this distributed network the activation of cortical midline structures (CMS) was reported most consistently (Kelley et al., 2002; Fossati et al., 2003; Northoff et al., 2006; Johnson et al., 2009; Lemogne et al., 2011; Qin and Northoff, 2011; D'Argembeau et al., 2012). Whereas frontal regions of the CMS have been associated with self-focused cognitive processes of evaluation and reappraisal (Ochsner et al., 2004; Northoff et al., 2006; Schmitz,

2007; Etkin et al., 2011), posterior parts within the CMS, namely the precuneus and the posterior cingulate cortex (PCC), are thought to link self-referential stimuli to past experiences (Fink et al., 1996; Cavanna and Trimble, 2006; Northoff et al., 2006). In addition, activation of the anterior insula has consistently been reported during emotional self-referential tasks (Modinos et al., 2009; Qin and Northoff, 2011). Considering an association between insula activation and the internally generated recall of subjective feelings and the evaluation of distressing cognitions (Phan et al., 2002; Craig, 2009), we hypothesise that enhanced insula activity will be observed during confrontation with self-critical stimuli. Furthermore, early emotion theories have already highlighted the critical involvement of the hippocampus–amygdala formation in emotional experiencing (Papez, 1937; MacLean, 1949). The hippocampus and amygdala are heavily interconnected (Pitkänen et al., 2006), and their interaction might be particularly important for the encoding of emotional events related to the self (Packard and Cahill, 2001; Phelps, 2004; Buchanan, 2007).

Processing of self-critical stimuli might not only involve the detection and reflexive experiencing of emotional evocation but could also involve the subsequent regulation of effective responses that preserve emotional control. Being confronted with unobtainable self-standards that are perceived as self-discrepancies, some might recruit reappraisal strategies for protecting the self. The ACC and the superior and inferior lateral frontal regions are assumed to play a central role in the top–down regulation of negative emotions by inhibiting and controlling the activation in limbic regions (Aron et al., 2004; Ochsner et al., 2004; Lieberman et al., 2007; Shackman et al., 2009). This top–down pathway seems to be centrally involved in successful emotion regulation, and there is growing evidence that the dorsolateral prefrontal cortex (dlPFC) is dysfunctional in its response to negative self-referential material in clinically depressed patients (Siegle et al., 2007; Hooley et al., 2009; Lemogne et al., 2009). Correspondingly, Hooley et al. (2005, 2009, 2012) showed that remitted depressed patients failed to activate the dlPFC, predominantly in the right hemisphere, when they heard tape-recorded critical utterances by their own mothers.

Excessive self-critical thinking may represent a psychological vulnerability to depressive symptoms (Sherry et al., 2013). Thus, examining neural activity and the potential risk and protective factors of depression during the processing of self-criticism in healthy subjects may contribute to a better understanding of the interaction between self-criticism and psychopathology. There is growing evidence suggesting a key role for right frontal brain areas in the distorted top–down pathway of dealing with criticism in depressed patients (Hooley et al.,

2012), but the influence of potential psychological moderators is unclear. Therefore, we investigated the association between activity in the right superior frontal areas during confrontation with self-critical stimuli and self-reported levels of depressive symptomatology, neuroticism, self-judgment and cognitive reappraisal. Mildly depressed mood, neuroticism and self-judgment have been suggested as vulnerability factors of depressive states (Teasdale and Dent, 1987; Neff, 2003). Cognitive emotion regulation skills, on the other hand, serve as protective factors and are linked to lateral frontal brain areas (Ochsner and Gross, 2008). Furthermore, recent studies with healthy subjects have reported a positive association between dlPFC activation, self-reported levels of self-criticism (Longe et al., 2010) and perceived criticism by others (Hooley et al., 2012). These results might reflect enhanced frontal control.

The main goal of this study was to further understand the neural basis of processing self-critical material. Differences in neural activity related to self-critical vs neutral stimuli (contrast 1) may also be attributed to differences in other properties of the stimuli such as human vs non-human, or negative/emotional vs neutral contents. To control for these potential factors we also contrasted self-critical stimuli with negative stimuli that do not have an individual self-referential meaning (contrast 2). This negative non-self-referential category contains stimuli that are negative and potentially self-referential (e.g., dishonest, stupid, unattractive) but were previously marked by the individual as not relevant for the self-concept. Furthermore, we tried to intensify emotional reactions via the use of individualised self-critical stimuli, and we assessed the neural correlates of dealing with perceived self-discrepancies. As we confronted participants with personally unpleasant stimuli, we expected to observe enhanced activity in regions associated with self-related emotional responses, namely the anterior insula and the hippocampus–amygdala formation. We also expected the anterior and posterior CMS, which are related to self-referential and autobiographical processing, to have elevated activity levels following stimulation (Northoff et al., 2006). We further hypothesised that the lateral frontal cortex regions and the ACC would be recruited in an attempt to moderate potential limbic responses to self-threatening material. Based on the available literature about the connections between psychological factors and neural activity described before, we hypothesised that during the processing of self-critical material subjects displaying high levels of depressive symptomatology, neuroticism, and/or self-judgment would exhibit more activity in their right superior frontal areas, whereas subjects displaying high levels of cognitive reappraisal would have reduced activity in these same areas.

Materials and methods

Participants

We recruited 20 healthy, right-handed adults (15 women and 5 men with a mean age of 30 years, s.d.: 10.2 years). The participants had no history of neurological or psychiatric illness and no history of drug or alcohol abuse. All participants were native German speakers. The study was approved by the local Ethics Committee, and all subjects gave written informed consent. Subjects' vision was normal or corrected to near normal using contact lenses. Subjects were reimbursed for their participation and time.

Stimuli

We used 24 neutral adjectives and 48 individually selected negative adjectives (24 with individual self-reference and 24 without). All adjectives consisted of 1–3 syllables and ≤ 12 letters. Using a German Word Database (<http://wortschatz.uni-leipzig.de>), we determined that all adjectives reached a frequency level of ≤ 20 , ensuring common use in the everyday language (frequency level based on Zipfs' law, which states that the reference word *the* [der] is 2^{20} times more frequent than the respective word). The 24 neutral stimuli (e.g., weekly, oval, cursive) were the same for all participants and were preselected by the authors from 100 potentially neutral words. Forty-two volunteers (21 women and 21 men) rated the valence of all adjectives using a scale ranging from -2 (very negative) to +2 (very positive). Twenty-four adjectives were selected based on the following criteria: modal value of 0, mean value between -0.20 and 0.20 and minimal standard error. The pre-selection of negative stimuli (e.g., fat, boring, jealous) was based on Anderson's list of personality-trait words (Anderson, 1968) and on the German word database. To cover the main classes of personal characteristics in German (Angleitner et al., 1990), we included adjectives from the following five categories: dispositions (temperament and character traits), abilities and talents, temporary conditions, social and reputational aspects and appearance. Furthermore, we ensured via a web-based and anonymous survey that we did not disregard any important aspects. Volunteers ($N = 41$, 24 women and 17 men) freely produced adjectives describing negative aspects of themselves or others without restrictions. Taking into account database studies and the free production of adjectives, we chose 52 negative prototypes, which covered the most important personality domains. As a final step, each prototype was supplemented with three synonyms that matched the same objective criteria. We assumed that

the synonyms likely activated the same specific self-schema as the prototypical adjective (Markus, 1977).

Before the fMRI assessment, each participant completed a set of questionnaires and a worksheet, allowing the participant to determine their individual set of self-critical adjectives at home. Subjects were instructed to mark all adjectives in the list of 52 prototypes that they experienced as unwanted self-discrepancies. Next, subjects were asked to select the six prototypes that fit themselves the most; they were also instructed to mark six prototypes that they evaluated as negative in other people but not in themselves. The six self-critical prototypes were rated in terms of their subjective strength of negative evaluation. The following question was asked: *‘how negative do you rate this characteristic of yourself?’* and responses were evaluated using a Likert scale ranging from 1 = not at all negative to 5 = very negative. Non-self-referential prototypes were rated in terms of how negative the person judges the respective characteristic in others. The question *‘how negative do you rate the characteristic in other people?’* was evaluated using the same Likert scale. Based on each person’s worksheet, individually tailored experiments were implemented using the Presentation software (Neurobehavioral Systems, <http://www.neurobs.com>). Stimuli were projected in the middle of a screen appearing on MRI-compatible goggles.

Experimental design

For each subject, we ran one session lasting ~12 min; this session included 24 blocks each lasting ~29 sec (**Figure 1**).

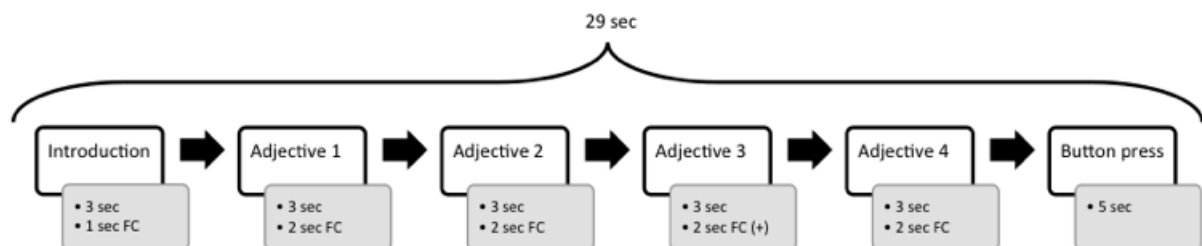


Figure 1 Schematic representation of one block including times of presentation (FC = fixation cross).

Four different types of blocks were presented in randomised order: six neutral blocks, six negative blocks with individualised self-critical adjectives, six blocks with individualised negative

adjectives that were not self-critical and six blocks of rest. During the rest blocks, participants were instructed to relax and look at the fixation-cross for 29 sec. A neutral block contained four of the 24 neutral adjectives presented in randomised order. Self-critical and negative blocks consisted of the six prototypes that were chosen by participants in advance, and these prototypes were interspersed with their three respective synonyms. Again, the order of presentation was completely randomised. During the experiment, each neutral or negative adjective was presented only once. During the measurement, participants were instructed to read the adjectives silently and focus on the meaning of the adjectives as well as on their triggered emotional reactions. Each block started with an introduction (3 sec) followed by a fixation cross (1 sec). The introduction varied depending on the respective condition (neutral: 'it is' ['oval']; negative non-self-referential: 'I am not' ['stupid']; self-critical: 'I am too' ['shy']). Subsequently, the four adjectives relating to a particular self-schema were presented. Each adjective was projected for 3 s and followed by a fixation cross for 2 sec. At the end of each block, participants were asked to press a specific button within a time period of 5 sec. This task served as a low-level attention task and ensured that participants focused on the presented stimuli. As the response rate was 100% we did not have to exclude any subjects due to non-responses. Before the scan protocol was initiated, subjects participated in a practice run with meaningless words.

Image acquisition and data analysis

fMRI scanning was performed at the University Hospital of Psychiatry (Zurich, Switzerland) using a 3-T Philips Intera whole-body MR unit equipped with an eight-channel Philips SENSE head coil. Functional time series were acquired with a sensitivity-encoded (Pruessmann et al., 1999) singleshot echo-planar sequence (SENSE-sshEPI). Thirty-six contiguous axial slices were placed along the anterior–posterior commissure plane covering the entire brain. A total of 247 T2*-weighted echo planar image volumes with blood-oxygen-level-dependent (BOLD) contrast (imaging parameters: repetition time = 3000 ms, echo time = 35 ms, 80 x 80 voxel matrix, interpolated to 128 x 128, voxel size = 2.75 x 2.75 x 4mm³, SENSE acceleration factor R = 2.0) were acquired. The first four scans were discarded due to T1 saturation effects. For each participant, a T1-weighted high-resolution image was acquired.

For data analysis, we used the SPM8 parametric mapping software (<http://www.fil.ion.ucl.ac.uk>). Standard pre-processing steps included correction for slice timing, realignment to the first image,

co-registration with the high-resolution T1-weighted image, normalisation into a standard stereotactic space (EPI template provided by the Montreal Neurological Institute, new voxel size = $2 \times 2 \times 2 \text{ mm}^3$), and smoothing with an 8-mm full width at half-maximum Gaussian kernel. First-level analysis was performed on each subject in a fixed-effect model including the six movement regressors (realignment parameters) and the three condition regressors. The BOLD data were modelled with a block design convolved with the standardised canonical haemodynamic response function and its temporal derivative. Estimated beta-parameters and *t*-contrast images (containing weighted parameter estimates) were brought to the second-level random effect analysis. For the fMRI data group analysis, contrast images were analysed using one-sample *t*-tests with age and gender as covariates. Regarding the whole-brain analyses of contrast 1 (self-critical > neutral) and contrast 2 (self-critical > negative non-self-referential), statistical images were assessed at $P = 0.001$ uncorrected (single voxel level) and reported for family-wise error (FWE) correction at the cluster level ($P = 0.05$). As our a priori hypotheses regarding the insula and the hippocampus–amygdala formation were specific enough, we reported activations for these structures that survived an uncorrected threshold of $P < 0.001$ on a whole brain level and were significant at $P < 0.05$ (FWE corrected at the cluster level) after small volume correction (SVC) using anatomical masks of the respective regions. For both contrasts, we applied an extent threshold of > 10 voxels. All coordinates are reported in MNI space. Brain regions were labeled according to the AAL toolbox (Automated Anatomical Labeling; Tzourio Mazoyer et al., 2002) implemented in SPM. For simple correlation analyses between psychometric self-reports and the BOLD signal, four Pearson correlations were calculated using the PASW Statistics 18.0 software package (IBM, Switzerland). Scores of depressive symptomatology, neuroticism, self-judgment and cognitive reappraisal were correlated with mean beta values of the a priori defined right superior frontal area. Significance levels were adjusted for multiple tests using the Bonferroni correction ($P < 0.0125$, one-tailed). Mean beta values were calculated using an in-house programmed MATLAB script. Anatomical masks for the SVC and the correlation analyses were based on the AAL atlas implemented in the WFU PickAtlas (Maldjian et al., 2003, 2004). Because we expected the hippocampus and the amygdala to be co-activated (Buchanan, 2007), we created one mask including both structures, which we referred to as the hippocampus–amygdala formation. The anatomical mask for the correlation analyses covered a broad right lateral frontal region including parts of Brodmann areas 6, 8, 9, 10 and 46. We extracted mean beta values from this entire brain region.

Psychometric data

Prior to scanning, participants completed a set of self-report questionnaires. To assess depressive symptomatology in a non-psychiatric population, a validated 15-item German short-version of the *Center for Epidemiological Studies Depression Scale* (CES-D; Radloff, 1977) was administered (*Allgemeine Depressionsskala - Kurzform*; Hautzinger and Bailer, 1993). In the CES-D participants are asked to appraise different symptoms of depression during the preceding 1-week-interval on a four-point-rating scale. Furthermore, subjects completed the 26-item German version of the *Self-Compassion-Scale* (SCS-D; Hupfeld and Ruffieux, 2011). Self-compassion entails being kind and understanding towards oneself in instances of pain or failure rather than being harshly self-critical (SCS; Neff, 2003). The questionnaire consists of the six subscales *Self-kindness*, *Self-judgment*, *Common humanity*, *Isolation*, *Mindfulness* and *Over-identification*. In this study, we were especially interested in the five-item *Self-judgment* subscale (e.g. ‘When I see aspects of myself that I don’t like, I get down on myself’) as it reflects harsh self-critical thinking towards oneself, and the four-item *Mindfulness* subscale (e.g. ‘When something painful happens I try to take a balanced view of the situation’). As the *Mindfulness* subscale captures cognitive reappraisal strategies as well as related emotion-focused strategies in response to adverse stimuli, we used this scale as a proxy for cognitive reappraisal. In the following we will refer to it as cognitive reappraisal rather than mindfulness. We used the German short version of the *Big Five Inventory* (BFI-K; John et al., 1991) to measure neuroticism as a risk factor of depression with four items (e.g. ‘I see myself as someone who is relaxed, handles stress well’, reversed scored item). The psychometric properties in the validation samples were satisfactory (Rammstedt and John, 2005). Distributions of the CES-D, *Neuroticism*, *Mindfulness* (cognitive reappraisal) and *Self-judgment* scales are available as **Supplementary material S1**.

Results

Behavioural data

Scores on the CES-D ranged from 1 to 11 (mean 4.55; s.d. 3.19), showing that participants’ mood scores generally fell within the normal, healthy range (Hautzinger and Bailer, 1993). The *Self-judgment* scores ranged from 1 to 3.25 (mean 2.19; s.d. 0.64), average scores indicating low to moderate self-judgment, the *Mindfulness* scores ranged from 2.25 to 4.25 (mean 3.28; s.d. 0.52),

indicating a distribution from low to high cognitive reappraisal (Neff, 2003). Sum scores of *Neuroticism* (BFI) ranged from 7 to 16 (mean 10.7; s.d. 2.39).

Assessment of individualised self-critical and negative non-self-referential adjectives

On the worksheet including 52 potentially self-critical adjectives, participants chose an average of 8.4 (s.d. = 2.4; min = 6; max = 14) self-critical adjectives. Categories, absolute values, percentages and negativity ratings of the twelve marked prototypes with the harshest self-critical and non-self-referential content are reported in **Table 1**.

Table 1 Absolute values (percentage) and negativity ratings of self-critical and negative non-self-referential adjectives in corresponding categories.

Categories	Absolute values (percentage)		Negativity rating	
	<i>self</i>	<i>others</i>	<i>self</i>	<i>others</i>
Dispositions	61 (50.83%)	36 (30.00%)	$M = 2.56$ ($SD = 0.69$)	$M = 3.36$ ($SD = 0.79$)
Social and reputational aspects	30 (25.00%)	56 (46.67%)	$M = 2.84$ ($SD = 0.95$)	$M = 4.10$ ($SD = 0.58$)
Temporary conditions	13 (10.83%)	10 (8.33%)	$M = 2.86$ ($SD = 1.52$)	$M = 3.10$ ($SD = 0.78$)
Abilities and talents	9 (7.50%)	10 (8.33%)	$M = 1.81$ ($SD = 1.13$)	$M = 3.22$ ($SD = 0.81$)
Appearance	7 (5.83%)	8 (6.67%)	$M = 2.33$ ($SD = 1.03$)	$M = 2.00$ ($SD = 1.10$)
Total	120 (100%)	120 (100%)	$M = 2.62$ ($SD = 0.68$)	$M = 3.62$ ($SD = 0.56$)

Most frequently, adjectives being selected by participants as personally critical belonged to the category dispositions. On the other hand, negative non-self-referential characteristics selected most frequently belonged to the category social and reputational aspects. Moreover, participants rated adjectives describing others as significantly more negative than adjectives describing themselves [$t(19) = 8.11$, $P < 0.001$].

FMRI data

Neural activity in response to self-critical material

Contrast 1 (self-critical > neutral) yielded multiple large clusters reaching our predefined statistical threshold (**Table 2**; **Figure 2**).

Table 2 Brain areas activated in contrast 1 (self-critical > neutral). Clusters significant at $P < 0.05$ after statistical correction (FWE correction at cluster level) are reported. Multiple peaks within the same label are shown on subsequent lines. Regions are labeled according to the AAL atlas. *Significant corrected P values shown after SVC.

Anatomical region	Hemisphere	Cluster size <i>Voxel</i>	t (df 17)	P corrected <i>Cluster-level</i>	MNI coordinates <i>x y z (mm)</i>		
Lateral superior frontal	Right	393	6.86	0.001	16	52	32
Medial superior frontal	Medial		4.27		-4	52	20
	Medial		3.92		-4	60	24
Medial superior frontal	Medial	592	5.35	0.000	10	38	46
	Medial		4.99		-6	34	52
	Medial		4.71		0	40	54
Middle frontal gyrus	Left	428	5.88	0.001	-48	22	34
Lateral inferior frontal (orbitalis)	Left		4.74		-48	28	-10
Lateral inferior frontal (triangularis)	Left		4.19		-52	24	0
Precentral gyrus	Right	302	5.3	0.005	40	4	48
Middle frontal gyrus	Right		5.2		40	20	42
Lateral inferior frontal (triangularis)	Right	575	6.54	0.000	56	22	-2
	Right		5.23		56	24	12
Lateral inferior frontal (orbitalis)	Right		5.12		40	24	-10
Middle temporal gyrus	Right	312	5.08	0.004	64	-16	-12
	Right		5.06		62	-24	-6
	Right		4.22		52	-24	-8
Cerebellum (crus II)	Left	411	5.36	0.001	-28	-74	-38
Insula	Right	56	5.03	0.017*	40	22	-10
	Right		4.56		28	24	-10
	Right		4.17		46	22	-2
	Right		4.06		28	18	-12
	Left	47	5.23	0.024*	-30	16	-12
	Left		4.99		-32	12	-10
Hippocampus-amygdala formation	Left	18	4.74	0.042*	-18	-12	-14
	Left		3.92		-14	-8	-18

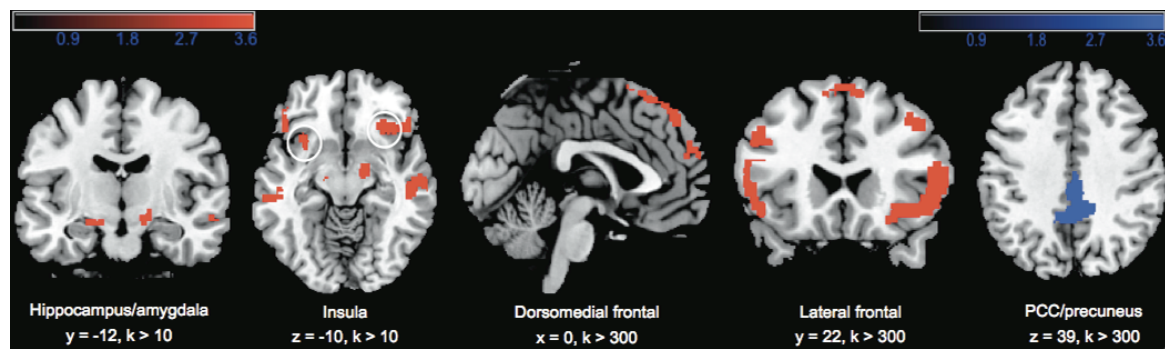


Figure 2 Increased BOLD responses in contrast 1 (self-critical > neutral) are depicted in red and contrast 2 (self-critical > negative non-self-referential) in blue ($P < 0.001$). Activations are overlaid on a canonical high-resolution structural image in MNI space. The color bars indicate statistical T variation. PCC = posterior cingulate cortex.

As hypothesised, confrontation with self-critical material elicited activation of the anterior insula and the hippocampus–amygdala formation. In addition, we found two activated clusters in medial superior frontal areas, extending to lateral superior parts of the right frontal lobe. Furthermore, the contrast evoked a significant increase in the BOLD signal in lateral areas of the bilateral inferior frontal cortex, including the pars triangularis and pars opercularis, extending to the orbital frontal cortex and parts of the middle frontal gyrus in both hemispheres. Moreover, we detected significant signal changes in the middle temporal gyrus (MTG) of the right hemisphere and in the left cerebellum (crus II).

Contrast 2 (self-critical > negative non-self-referential) revealed a significant cluster of activation in the medial PCC with a peak value in the left hemisphere and extending to parts of the precuneus (**Table 3; Figure 2**). The reverse contrast (negative non-self-referential > self-critical) did not reveal any suprathreshold clusters. Furthermore, contrasting the negative non-self-referential condition with the neutral condition (negative non-self-referential > neutral) did not show significant changes in brain activity.

Table 3 Brain areas activated in contrast 2 (self-critical > negative non-self-referential). Clusters significant at $P < 0.05$ after statistical correction (FWE correction at cluster level) are reported. Multiple peaks within the same label are shown on subsequent lines. Regions are labeled according to the AAL atlas.

Anatomical region	Hemisphere	Cluster size Voxel	t (df 17)	P corrected Cluster-level	MNI coordinates x y z (mm)		
Posterior cingulate cortex	Left	1294	6.79	0.000	0	-34	28
	Right		6.25		2	-40	16
Precuneus	Left		4.67		-4	-50	40

Correlation of signal changes with psychometric self-reports (contrast 1)

Self-reported neuroticism correlated positively with activation in the right superior frontal area [$r(20) = 0.524$, $P = 0.009$]. In contrast, self-reported cognitive reappraisal correlated negatively with activity in the same area [$r(20) = -0.507$, $P = 0.011$]. Correlations between scores of depressive symptomatology and activation of the right frontal cortex did not reach significance (significance level of $P < 0.0125$, Bonferroni corrected), although we observed a trend in the predicted direction [$r(20) = 0.378$, $P = 0.050$]. The expected association with levels of self-judgment did not surpass our predefined statistical threshold [$r(20) = -0.288$, $P = 0.109$].

Discussion

This study aimed to explore the neural correlates of processing individually tailored self-critical stimuli in healthy subjects. We observed enhanced activation of the hippocampus–amygdala formation and anterior insula when individuals were confronted with self-chosen self-critical adjectives, both structures implicated in emotional responses. Furthermore, healthy subjects seem to apply cognitive emotion regulation strategies via enhanced recruitment of an extended lateral frontal brain network, and they exhibited enhanced activation in the anterior and posterior CMS, which are related to self-referential and autobiographical memory processes.

At the behavioural level, participants rated adjectives describing others as significantly more negative than adjectives related to the self. The above-average effect could provide an explanation for this finding as people have a pervasive tendency to believe that they are better

than others in a multitude of ways (Chambers and Windschitl, 2004) and process feedback in a positively biased way (Korn et al., 2012). This widely replicated bias is thought to be driven by strivings for self-enhancement and mood maintenance (Alicke, 1985; Taylor and Brown, 1988; Taylor and Armor, 1996), and this strategy may be a healthy way of dealing with ego-threats.

Contrasting self-critical with neutral stimuli (contrast 1) revealed activation in the anterior insula and the hippocampus–amygdala formation, likely reflecting an emotional response to individualised self-critical material. While, the hippocampus and the amygdala are considered to be co-activated following emotional arousal and retrieval of emotional past experiences (Buchanan, 2007), the anterior insula is recognised for monitoring internal states related to emotional experiences that emerge as conscious feelings (Damasio et al., 2000). Interestingly, Longe et al. (2010) reported insula activation following self-reassurance but not following self-criticism, suggesting that the process of self-criticism may have a more external focus and may exclusively rely on top-down neural processing. A possible explanation for the differing outcomes regarding activation of the insula and limbic structures may be an enhanced emotional involvement during the present task, as participants were not confronted with standardised situation scenarios but individually tailored unpleasant stimuli.

Furthermore, contrast 1 also revealed large bilateral activations of superior and inferior lateral frontal regions. Previous studies reported involvement of the lateral inferior (Aron et al., 2004; Ochsner et al., 2004; Phan et al., 2005; Johnstone et al., 2007) and superior (Davidson, 2000; Ochsner et al., 2002; Phan et al., 2005; Shackman et al., 2009) frontal cortex during inhibition and cognitive emotion regulation. These structures are frequently co-activated during reappraisal and voluntary suppression of negative stimuli, and they are assumed to modulate cortical and subcortical structures (e.g., insula, amygdala and hippocampus) that are involved in emotion experiencing and that are specifically activated in relation to subjective ratings of emotional intensity (see Ochsner and Gross, 2008 for an overview). In previous studies, the superior prefrontal cortex was associated with maintaining and manipulating emotional information in working memory during reappraisal (Northoff et al., 2006; Ochsner and Gross, 2008), and the inferior part seems to be associated with selecting appropriate reappraisals (Denny et al., 2009). Therefore, we conclude that the observed pattern of superior and inferior lateral frontal co-activation might reflect cognitive control for adaptively dealing with self-discrepancies, and this activation may prevent individuals from feeling overwhelmed by negative emotions. Interestingly, Lieberman et al. (2007) reported that the right lateral inferior cortex

plays a prominent role in the framework of affect labeling. Given that participants in this study were instructed to silently read the words in their heads, the process of putting feelings into words and thereby applying strategies of affect labeling might have facilitated the reappraisal of threatening material.

Furthermore, we observed activations in the right MTG and the left cerebellum. Anderson et al. (2004) studied brain regions associated with the inhibition of unwanted memories and found evidence that lateral frontal regions interact with the medial temporal lobe in an attempt to suppress memory recollection. The MTG may therefore support the inhibitory pathway mentioned above. Likewise, the crus II of the left cerebellum, an area strongly interlinked with prefrontal areas, is often reported to be co-activated during emotional and cognitive paradigms, as determined by enhanced BOLD signals in this region (Stoodley and Schmahmann, 2009). We could not detect significant differences comparing the negative with the neutral condition. This suggests that the effect of self-critical processing may go beyond mere negativity.

To control for differing attributes of the stimuli other than self-critical properties (e.g., human vs non-human, or negative/emotional vs neutral), we ran a second contrast (contrast 2, self-critical > negative non-self-referential). This contrast revealed activations in the PCC and in the left precuneus. As participants rated the negative non-self-referential adjectives as more negative than the self-critical adjectives, we also ran the reverse contrast (negative non-self-referential > self-critical). This contrast did not show any significant activation. We argue that evaluative processes related to self-critical attributes differ from evaluative processes related to negative characteristics of other people in intensified recall processes of compatible memories. Previous findings demonstrating that posterior regions of the CMS are strongly involved in episodic memory retrieval (Fink et al., 1996; Cavanna and Trimble, 2006; Northoff et al., 2006; Svoboda et al., 2006; Cabeza and St Jacques, 2007) and studies showing the brain's ability to distinguish real from imaginary memories (Hassabis et al., 2007) are consistent with this interpretation. In addition, activity could also capture differences in emotional intensity due to enhanced self-relevance.

We examined the links between potential risk and/or protective factors of clinical depression and neural activation during confrontation with self-critical stimuli, and we observed a positive association between neuroticism and right superior frontal activity. We also observed a negative association between self-reported cognitive reappraisal and neural activity in the same areas.

These results may indicate that highly neurotic yet healthy people require stronger right frontal cortex activation to regulate their negative feelings associated with self-criticism. Conversely, people using cognitive reappraisal strategies more frequently may not need to recruit this region to the same degree to achieve the same level of regulation. Cumulatively, we conclude that without other instructions, healthy people likely apply reappraisal strategies via the activation of a broad lateral frontal network. In addition, the degree of right frontal activation might be moderated by personality traits such as neuroticism and habitual use of cognitive reappraisal strategies. This important modulating mechanism is active in healthy persons but could be less apparent in clinically depressed patients, resulting in failure to activate dlPFC during confrontation with self-referential material (Lemogne et al., 2009), in response to emotional information (Siegle et al., 2007), and during the processing of critical remarks (Hooley et al., 2005, 2009, 2012). This might explain the fact that even after complete remission, formerly depressed individuals experience stronger negative feelings in response to personally significant threats (Hooley et al., 2005, 2009, 2012).

The main limitation of this study lies in the exclusive attribution of the reported activity to self-critical processing. Whereas contrast 2 controlled for stimuli differences such as humanness and negativity, this contrast still fails to control for differences due to self vs other related processing irrespective of valence. To further enhance specificity, an additional condition containing positive self-views would be helpful. Other limitations worth mentioning include first, that the current findings are limited to healthy individuals. To further investigate clinically relevant alterations of the top-down pathway in the context of self-criticism, future studies should include clinically depressed patients. Second, we did not assess information concerning the subjects' experiences in the scanner. Self-reports about potential mood repair strategies (e.g., reappraisal, self-reassurance, mindful regulation) would provide useful additional information about participants' top-down strategies. Third, some concerns may be raised regarding the utilised self-report measures as future studies should cover both constructs, neuroticism and cognitive reappraisal, more broadly using multiple measures. Furthermore, given that the right superior frontal region covers a wide anatomical area, a more detailed anatomical specification is required to better understand the roles of personality factors in relation to the activity of specific subsections of this anatomical area.

In summary, the present findings highlight various aspects of self-criticism processing in healthy subjects, including self-referential processing, evoked emotional responses, associated

regulatory processes (contrast 1) and self-specific memory processes (contrast 2). Specifically, our data support the central involvement of a broad lateral frontal network in subjects' dealing with provoked emotional responses, possibly reflecting the recruitment of cognitive reappraisal strategies. Furthermore, right superior frontal areas were moderated by levels of neuroticism and cognitive reappraisal, further supporting the potential clinical relevance of these areas.

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Supplementary material:

S1: Absolute frequency distribution of the four scales (N = 20).

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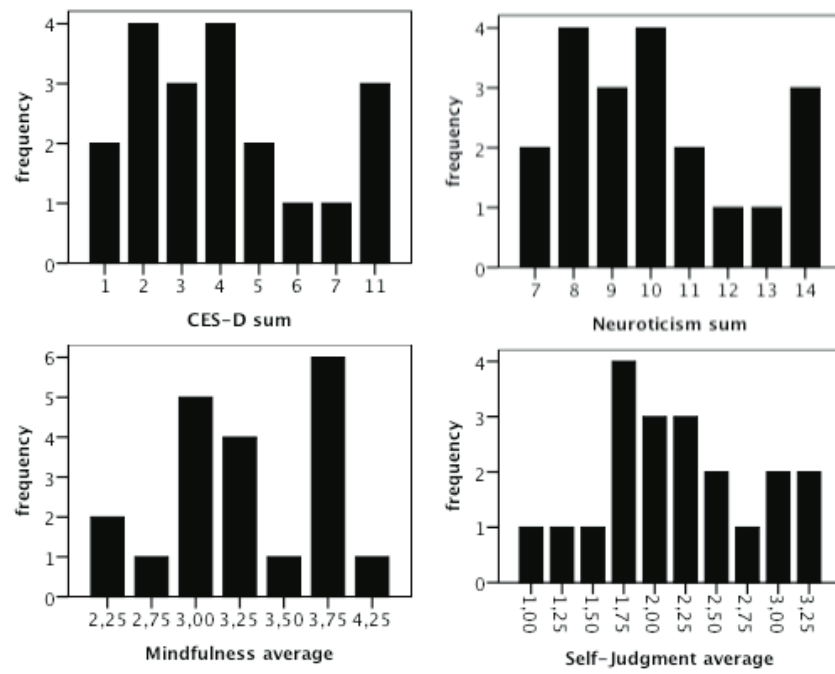
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Supplementary material



S1 Absolute frequency distribution of the four scales (N = 20). The Mindfulness subscale was used as a proxy for cognitive reappraisal.

Amygdala Response to Individualized Self-Critical Stimuli Predicts Emotional-Skill Acquisition and Symptom Improvement in Psychotherapy for Depression

Nadja Doerig,^{1,7} Tobias Krieger,¹ David Altenstein,¹ Yolanda Schlumpf,² Simona Spinelli,^{3,7,8} Jakub Späti,⁴

Janis Brakowski,⁶ Boris B. Quednow,^{5,7,8} Erich Seifritz,^{6,7,8} Martin Grosse Holtforth^{1,3,9}

¹ Research Section Psychotherapy for Depression, Department of Psychology, University of Zurich, Switzerland.

² Division of Neuropsychology, Department of Psychology, University of Zurich, Switzerland.

³ Preclinical Laboratory for Translational Research into Affective Disorders, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Switzerland.

⁴ Department of Psychophysiology, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan.

⁵ Experimental and Clinical Pharmacopsychology, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Switzerland.

⁶ Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Switzerland.

⁷ Neuroscience Center, University and ETH Zurich, Switzerland.

⁸ Zurich Center for Integrative Human Physiology, University of Zurich, Switzerland.

⁹ Division of Clinical Psychology and Psychotherapy, Department of Psychology, University of Bern, Switzerland.

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Abstract

Objective: A better understanding of brain responses to emotional stimuli and their associations with psychotherapy outcome may enhance psychological treatments for depressed patients. **Method:** fMRI data were collected prior to individual cognitive-behavioral therapy (CBT). Dysfunctional cognitions and emotional skills were assessed before and after treatment and at 3-month follow-up. We studied 23 currently unmedicated depressed outpatients and 28 healthy control participants. Twenty-one patients were included in the outcome-prediction analyses. Differences in amygdala and ventral-striatum activity between patients and controls and between therapy responders and non-responders were identified. Pre-treatment brain activity was correlated with treatment response. Cognitive and emotional changes were analyzed as potential mediators between neurophysiological predictors and treatment response. **Results:** Patients showed an enhanced activity in the amygdala and the ventral striatum compared to controls. Non-responders (N = 8) showed an enhanced activity in the right amygdala compared with responders (N = 13), and better outcome was predicted by lower activity in the right amygdala in response to self-critical material before treatment. Emotional, but not cognitive changes fully mediated the association between right amygdala activity and treatment response at post and follow-up. **Conclusions:** An enhanced activity in the right amygdala is associated with the processing of self-critical material in patients responding poorly to CBT. This relationship might be explained by amygdala hyperactivity possibly impeding the acquisition of emotional skills during psychotherapy.

Introduction

Harsh self-criticism not only triggers strong negative emotional responses but is also a symptom of depression itself. Accordingly, pervasive self-critical thinking is considered a risk factor for the development and maintenance of depression (Zuroff et al., 1990) and is consequently an important change target in the psychotherapy for depression (Beck et al., 1979). Cognitive-behavioral therapy (CBT) is an empirically supported intervention that is efficacious in the acute treatment of major depressive disorder (MDD) (Driessen & Hollon, 2010). However, a large proportion of patients fail to achieve an adequate response (Little, 2009).

The identification of neural abnormalities in MDD during self-critical processing and the search for related neurophysiological markers of outcome prediction might advance differential treatment selection. In this study, we further examine the potential psychological mechanisms linking neural markers to psychotherapy outcomes. This integrative neurophysiological-psychological strategy may help optimize individualized treatment strategies for depressed patients.

A wide range of studies has examined brain activity related to disturbances of emotional and cognitive processing in depression (Diener et al., 2012). Altered amygdala and striatal function is thought to contribute to the mediation of emotional responses in acutely depressed patients (Drevets et al., 2008). However, previous findings have been inconsistent (Mayberg, 2003; Townsend et al., 2010). The majority of related fMRI studies have used standardized emotional pictures, masked or unmasked facial stimuli, or personally relevant rating tasks for examining neural responses to emotional stimuli (see Townsend et al., 2010 for an overview). The few studies that confronted participants with individualized emotional stimuli reported sustained amygdala activity (Siegle et al., 2002) and enhanced activity in the amygdala and ventral striatal regions (Kessler et al., 2011) in depressed patients compared to healthy controls. Moreover, passive processing of emotional visual stimuli is associated with a higher probability of amygdala activation than processing accompanied by active task instructions (Costafreda et al., 2008). A previous study has already shown enhanced amygdala activity during confrontation with individualized self-critical stimuli compared to neutral stimuli in a healthy sample (Doerig et al., 2013). Accordingly, methodological heterogeneity regarding individualization of stimuli and the mode of presentation might explain some of the mixed findings, in addition to heterogeneous symptomatic profiles, medication status, differences in levels of depression severity, or comorbid

anxiety disorders (Townsend et al., 2010). Consequently, the study of striatal and particularly amygdala abnormalities in response to individualized painful self-critical stimuli in unmedicated depressed patients may yield more ecologically valid results.

Functional magnetic resonance imaging (fMRI) assessment has been suggested as a powerful strategy for identifying prognostic markers of clinical response (Fu et al., 2013). Using a meta-analytic approach, Fu and colleagues (2013) found enhanced activity in the right striatum and the anterior insula associated with a lower likelihood of clinical benefit from treatment including CBT and medication therapy. However, previous studies on amygdala response have yielded heterogeneous results regarding outcome prediction. Related findings have indicated increased baseline amygdala activation in subsequent responders but have also shown the reverse relationship with increased amygdala activity associated with poor therapy outcome during the treatment of depression and post-traumatic stress disorder (PTSD; Bryant et al., 2008). Moreover, several studies have also reported no significant relationship between amygdala activity and outcome (see Fu et al., 2013 for an overview).

In accordance with the results of studies utilizing individualized emotional stimuli, we hypothesize enhanced responses in the ventral striatum and the amygdala in depressed patients compared to matched healthy control subjects. In addition, we explored the differences between therapy responders and non-responders, as well as the potential prediction of treatment outcome by differential activity in these subcortical regions. If such predictions were verified, we then set out to explore the associated psychological change mechanisms. Psychological change mechanisms are defined as those therapy processes that have the potential to ameliorate psychopathology (Hollon et al., 2002). Among others, change in dysfunctional cognitions as well as the acquisition of emotional skills have been identified as psychological change mechanisms that are associated with better CBT outcomes (Fehlinger et al., 2012; Furlong & Oei, 2002). Consequently, we set out to examine whether the potentially identified biomarker-outcome relationships would be mediated by changes in dysfunctional cognitions and/or by acquisition of emotional skills.

Methods

Subjects

We investigated a sample of patients with a current major depressive episode (MDE; $N = 23$), and a sample of healthy control subjects ($N = 28$). All participants were right-handed, native German speakers and showed no contraindication to MR imaging. The study procedure has been approved by the local Ethics Committee, and all participants provided advance written informed consent after complete description of the study. Treatment was free of charge, and participation in the fMRI assessment was reimbursed according to local standards. Patients were recruited from a larger study on cognitive-emotional processing in psychotherapy. The fMRI data of six healthy control participants had been analyzed for a previous publication (Doerig et al., 2013).

To qualify for the study, patients were required to have a minimum score of 14 on the Beck Depression Inventory-II (BDI-II) at screening (Hautzinger et al., 2006). Average depression severity at baseline was moderate, with a mean BDI-II score of 26.6 ($SD \pm 9.3$). MDE diagnoses were confirmed by the *Structured Clinical Interview* for DSM-IV (Wittchen et al., 1997). Diagnostic exclusion criteria included history of mania or psychotic symptoms, borderline, antisocial or schizotypal personality disorder, and current substance dependence. Most of the patients (70%) were diagnosed with a recurrent MDE, whereas the remaining 30% met criteria for a first MDE. Other comorbid diagnoses, including anxiety disorders (39%), were acceptable as long as depression was the primary treatment focus. The patients did not take concurrent psychotropic medication for at least four weeks prior to the scan sessions and remained medication-free throughout the treatment and 3-month follow-up period. In total, 24 MDD subjects were scanned. One patient was excluded for further analysis due to lack of motivation and strong discomfort during the scan. Thus, the data of 23 patients (11 women; mean [SD] age = 37.4 [± 17.1] years) were included.

Healthy controls had no personal or first-degree relative history of MDD and no self-reported psychiatric problems (13 women, mean [SD] age = 35.6 [± 12.6] years). MDD and control groups did not differ in age ($P = .60$), sex distribution ($P = .92$), marital status ($P = .44$), or highest level of education ($P = .17$).

After comparing the neural activity of the healthy subjects with that of the depressed subjects, we further examined differential brain activity at baseline between the CBT responders and non-

responders and studied eventual links with therapy outcomes. Two patients withdrew from the treatment before completing the 22 sessions (sessions 15 and 19) and were not included in the prediction analysis. The resulting patient sample size was $N = 21$ (10 women; mean [SD] age = 38.3 [± 12.4] years). Another three patients had missing data at follow-up.

Psychometric measures

For the depressed sample, assessment of depressive symptom severity was measured using the German version of the 21-item BDI-II (Hautzinger et al., 2006). For the assessment of emotion-regulation skills we used the total score of the 27-item German version of the Emotion-Regulation Skills Questionnaire (ERSQ; Berking & Znoj, 2008). Furthermore, dysfunctional cognitions were assessed using the 40-item German version of the Dysfunctional Attitude Scale (DAS; Hautzinger et al., 1985). To control for trait anxiety, we used the 20-item trait form of the State-Trait Anxiety Inventory (STAI; Laux et al., 1981).

Procedure

Psychotherapy was offered as a research therapy separate from routine care in the outpatient clinic of the University's psychology department. All patients were scanned before the onset of their 22 weekly individual CBT treatment sessions.

Depressive symptoms were assessed before therapy at baseline (pre), directly after termination (post) and three months after therapy end (follow-up). We defined the response to treatment as a minimum pre-post reduction of 50% in BDI-II scores (Frank et al., 1991). Assessments of the ERSQ and the DAS took place both immediately prior to and after treatment. Trait anxiety was assessed at baseline.

Stimuli and task

During the fMRI-measurement, participants were presented with three different types of adjectives in six 29-second blocks of four adjectives each: neutral adjectives, individualized self-critical adjectives, and individualized negative adjectives that were not self-critical. Furthermore, 29-second blocks of rest (looking at a fixation cross) were inserted randomly. Each block contained an introduction indicating the condition (neutral, negative, self-critical) followed by

the presentation of the four adjectives and a request to press a button. **Figure 1** shows the presentation times.

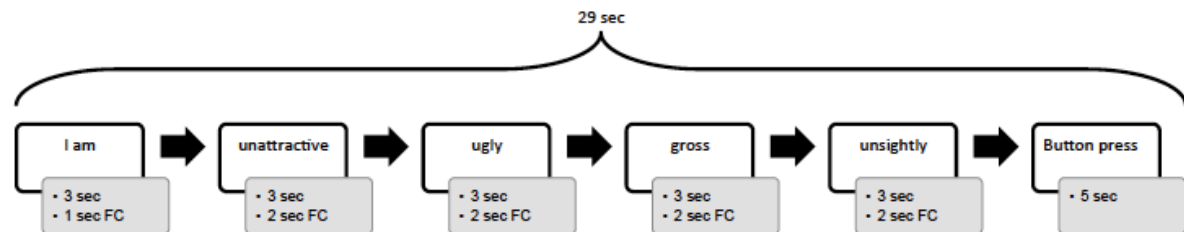


Figure 1 Example of a self-critical block including presentation times of a participant choosing the prototype “unattractive” as self-critical. FC = fixation cross.

For each subject, we ran one session lasting approximately 12 minutes. The order of presentation was completely randomized. Individualized self-critical and negative non-self-critical blocks consisted of prototypes (e.g., fat, boring, jealous) that subjects chose individually out of a list of 52 negative attributes. During the imaging experiment, prototypes were presented interspersed with their three respective synonyms that were assumed to activate the same self-schema. Participants were instructed to read the adjectives silently and focus on the meaning of the adjectives, as well as on the triggered emotional reactions. For more details on the stimuli and their assessment, see our previous study (Doerig et al., 2013).

Imaging

Structural and Functional Image Acquisition

The fMRI scanning was performed at a university psychiatric hospital in Switzerland using a 3-Tesla Philips Intera whole-body MR unit equipped with an 8-channel Philips SENSE head coil. Functional time series were acquired with a sensitivity-encoded (Pruessmann et al., 1999) single-shot echo-planar sequence (SENSE-sshEPI). Thirty-six contiguous axial slices were placed along the anterior-posterior commissure plane covering the entire brain. A total of 247 T2*-weighted echo planar image volumes with blood-oxygen-level-dependent (BOLD) contrast (imaging parameters: repetition time = 3000 ms, echo time = 35 ms, 80x80 voxel matrix, interpolated to 128x128, voxel size = 2.75x2.75x4 mm³, SENSE acceleration factor R = 2) were acquired. The first

four scans were discarded due to T1 saturation effects. For each participant, a T1-weighted high-resolution image was acquired.

Data Preprocessing and Statistical Analysis

The functional image data were pre-processed and analyzed in SPM8 (Wellcome Department of Imaging Neuroscience) and implemented in Matlab using standard pre-processing steps (Friston et al., 2011). First-level analysis (fixed effects) was performed on each subject including the six movement regressors and the three condition regressors. The BOLD data were modeled with a block design convolved with the standardized canonical haemodynamic response function and its temporal derivative. Estimated beta-parameters and t-contrast images were brought to the second-level analysis (random effects). For both fMRI data group analyses (patients vs. controls; responders vs. non-responders), images of the contrast of interest (self-critical vs. neutral) were analyzed using two-sample t-tests. A voxel-wise threshold of $P < .001$, requiring >10 contiguous voxels was applied. According to our a priori hypotheses, we reported amygdala and striatal structures significant at $P < .05$ FWE corrected at the cluster level after small volume correction (SVC) using the anatomical masks of the respective regions (WFU-PickAtlas) (Maldjian et al., 2004; Maldjian et al., 2003). All coordinates are reported in MNI space and peak activations were labeled according to the Automated Anatomical Labeling (AAL)-atlas (Tzourio Mazoyer et al., 2002). Analyses of socio-demographic data (χ^2 -test) were performed to ascertain comparability of the two respective groups.

To examine change in depressive symptoms independent of initial severity, residual gain scores were calculated from a regression of pre-treatment BDI-II-scores on post and follow-up scores (Bryant et al., 2008; Siegle et al., 2006). Associations of possible predictors and outcome were analyzed using Pearson correlations (two-tailed) between the BOLD signal extracted from 6 mm radius spheres around peak voxels from the responder-analysis and residual BDI-II gain scores at post and follow-up. Mean beta parameter estimates were extracted using an in-house programmed Matlab script.

Mediation analyses were calculated using the PROCESS script by Preacher and Hayes (Preacher & Hayes, 2004). A total effect (c) of an independent variable (IV) on a dependent variable (DV) is composed of a direct effect (c') of the IV on the DV and an indirect effect of the IV on the DV through a proposed mediator (M). The indirect effect was computed by bootstrapping re-sampling with 1000 samples. We considered point estimates of the indirect effects as significant

in case zero was not included in the 95% confidence interval. We used residual BDI-II gain scores at post and follow-up as dependent variables. Potential mediator variables were residual DAS and ERSQ gain scores, reflecting changes in cognitive and emotional processes during therapy. Correlation and mediation analyses were performed in PASW Statistics 18.0 (IBM Switzerland).

Results

Cross-sectional analyses

Baseline differences in brain activity between healthy control subjects and MDD patients

Cortical group differences at whole brain level are reported in the supplement (**S1**). According to our hypotheses, MDD patients showed enhanced activity in the left amygdala (coordinates: -22, -6, -16; $t_{49} = 4.05$, $\kappa = 21$), the bilateral putamen (right [coordinates: 36, 0, -4; $t_{49} = 4.13$, $\kappa = 31$] and the left [coordinates: -32, -10, 4; $t_{49} = 3.93$, $\kappa = 20$]) and right caudate nucleus (coordinates: 6, 12, -2; $t_{49} = 4.63$, $\kappa = 80$; coordinates: 20, 26, 0; $t_{49} = 4.09$, $\kappa = 14$), surviving SVC at $P < 0.05$ (**Figure 2A & 2B**).

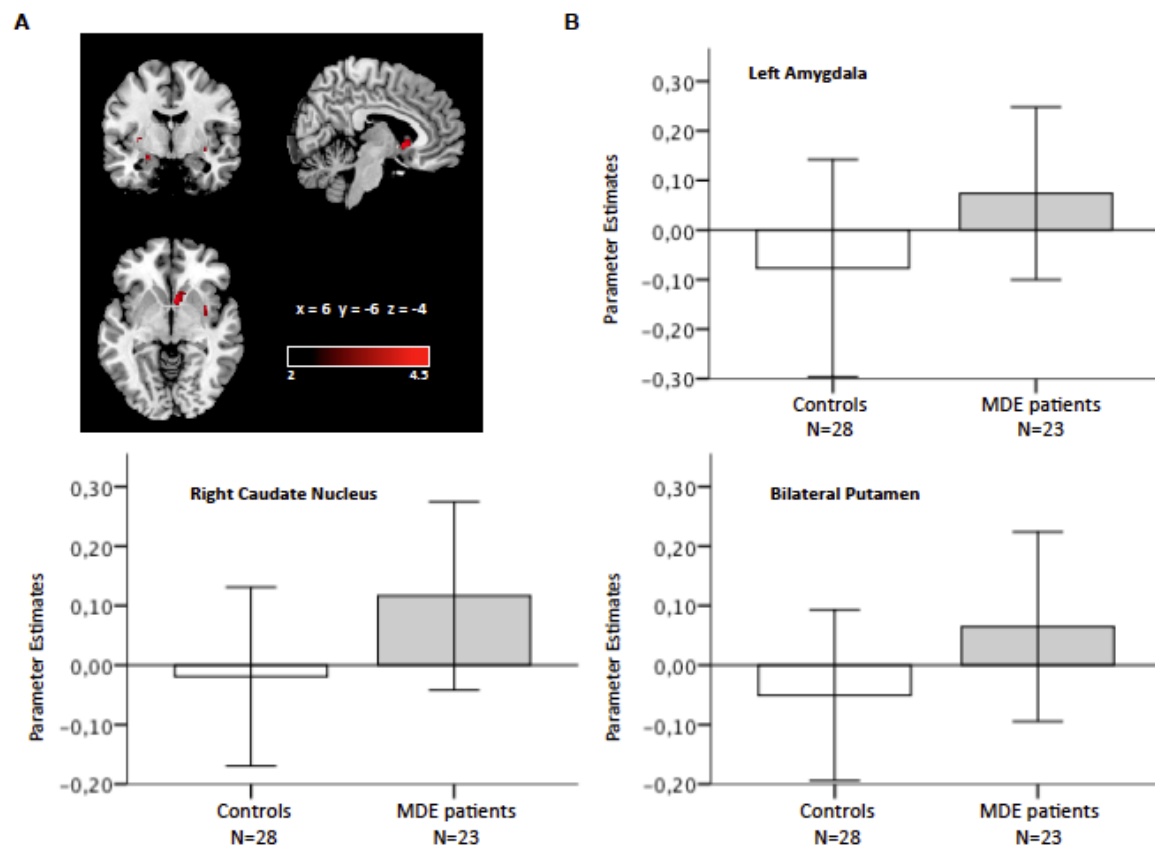


Figure 2 A: Enhanced activity in the amygdala and striatum ($P < .001$, $\kappa > 10$) in patients compared to controls. **B:** Plotted mean beta parameter estimates (Eigenvariates) and standard deviations of contrast images (self-critical vs. neutral) in controls and depressed patients.

Prediction analyses

Clinical Response

Applying the 50%-criterion for treatment response, 13 patients were considered treatment responders and eight patients were considered non-responders (**Table 1**).

Table 1 Psychometric data of CBT responders and non-responders at time-points pre, post, and 3-month follow-up. Means, and standard deviations and p values are given.

	Responders (N=13)	Non-responders (N=8)	P Value
BDI-II pre	27.85 [8.44]	26.13 [10.39]	.68
BDI-II post	6.23 [5.54]	21.25 [7.19]	<.001***
BDI-II 3-month follow-up	8.30 [7.62] (N=10)	19.75 [15.00]	.051
ERSQ pre	79.36 [12.38]	71.13 [13.30]	.16
ERSQ post	109.12 [12.54]	75.88 [14.97]	<.001***
DAS pre	132.23 [23.97]	115.25 [31.04]	.18
DAS post	112.67 [28.60] (N=12)	121.15 [23.89]	.50
STAI trait pre	60.01 [9.62]	56.13[12.63]	.42

At baseline, there were no statistically significant differences between responders and non-responders regarding sex distribution ($P = .86$), age ($P = .98$), marital status ($P = .63$), highest educational level ($P = .22$), single or recurrent episodes ($P = .75$), chronicity ($P = .92$), or comorbid anxiety disorder ($P = .60$). Whereas there were no significant differences in all measures at baseline between the groups, there were significant differences at post for the BDI-II and the ERSQ (**Table 1**).

Baseline differences in brain activity between CBT responders and non-responders

Non-responders and responders differed only in the right amygdala (coordinates: 26, 2, -20; $t_{19} = 4.30$, $\kappa = 19$), with non-responders showing enhanced activity, surviving SVC at $P > 0.05$ (**Figure 3A & 3B**). Because amygdala activity might be related to depression severity (Drevets et al., 1992) or anxiety (Stein et al., 2007), we included in a further step BDI-II pre, trait anxiety, or comorbid anxiety as covariates of interest in the between-group analysis. This affected the results only slightly (**S2**). No differences in the activation of striatal regions were detected. Moreover, responders did not show higher activity in any regions than CBT non-responders.

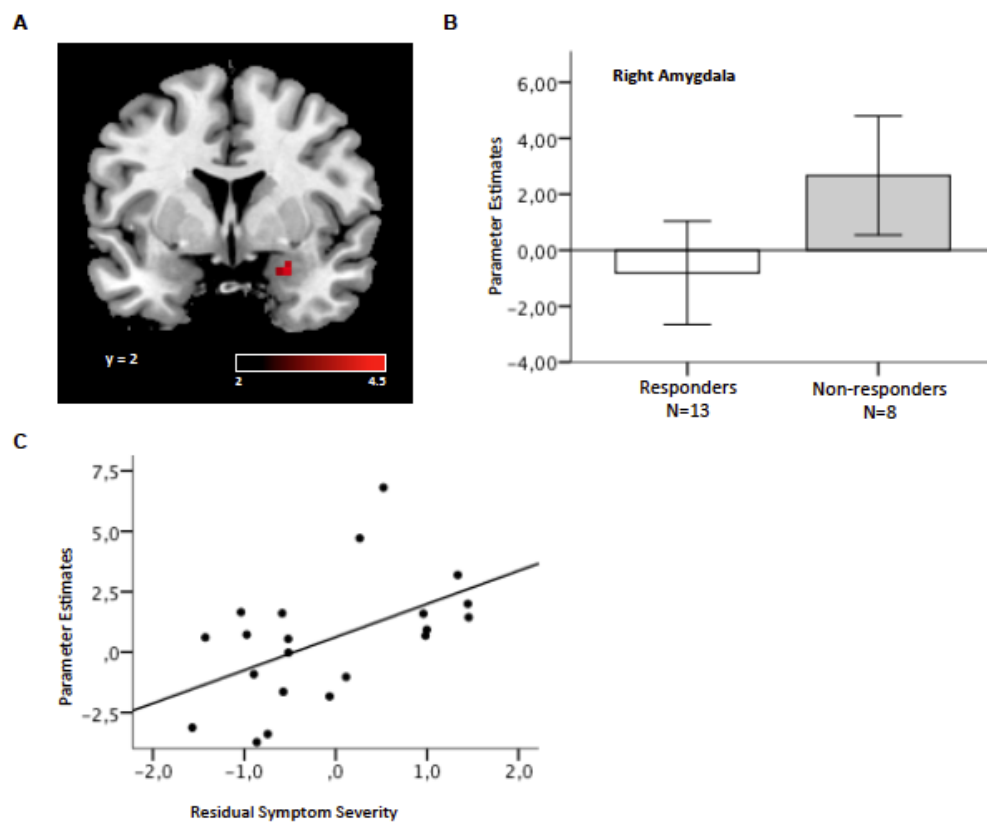


Figure 3 A: Enhanced activity in the right amygdala in non-responders compared to responders ($P < .001$, $\kappa > 10$). **B:** Plotted mean beta parameter estimates (Eigenvariates) and standard deviations of contrast images (self-critical vs. neutral) in responders and non-responders. **C:** Relationship between right amygdala activity (parameter estimates) and z-standardized residual BDI-II gain scores post (residual symptom severity).

Association of baseline neural activity in the right amygdala and treatment response

The BOLD response in the right amygdala during confrontation with self-critical material correlated positively with residual BDI-II gain scores at post-treatment ($N = 21$; $r = 0.52$, $P = .02$) (**Figure 3C**) and follow-up ($N = 18$; $r = 0.53$, $P = .02$). Therefore, poor responses to CBT were significantly associated with increased right amygdala recruitment during the processing of self-critical material.

Mediation analysis explaining attenuated therapy outcome

To explain the association between amygdala activity and negative outcome in CBT, we evaluated the change of dysfunctional cognitions and the change in emotional skills as theoretically derived and empirically supported mechanisms of change that may be compromised by amygdala hyperactivity. In the related mediation analysis, the association

between right amygdala activity before therapy and residualized depression scores post-therapy was mediated by emotional-skill acquisition. After controlling for emotional-skill acquisition, the relation between amygdala activity and outcome was no longer significant, indicating full mediation (**Figure 4**).

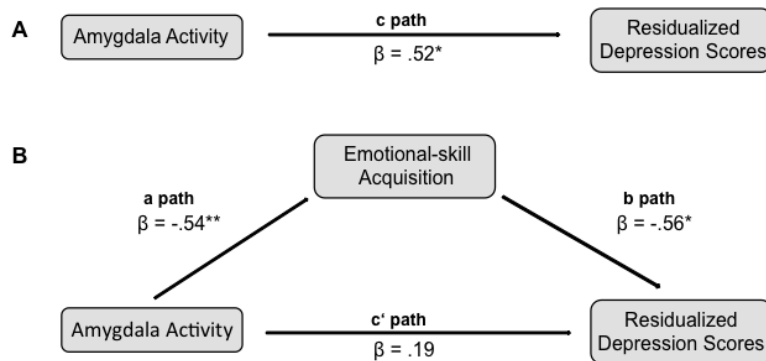


Figure 4 Mediation path model of right amygdala activity (mean beta values), residual symptom severity post and emotional-skill acquisition. Standardized regression coefficients (β) for the direct (**A**) and the indirect (**B**) paths are given. * $P < .05$. ** $P < .01$.

This effect survived introduction of comorbid anxiety and/or trait anxiety as covariates. Furthermore, we also found a similar mediation effect when the residual BDI-II gain score at follow-up was the DV. In contrast, there was no mediation by change of dysfunctional attitudes at post and follow-up (**Table 2**).

Table 2 Summary of mediation analyses.

Independent variable (IV)	Mediating variable (M)	Dependent variable (DV)	Effect of IV on M (a)	Effect of M on DV (b)	Direct effect (c')	Indirect effect (ab)	Total effect (c)	N
Amygdala activity	ERSQ	BDI-II post	$\beta = -.54^{**}$	$\beta = -.56^*$	$\beta = .19$	$\beta = .30^a$	$\beta = .52^*$	21
Amygdala activity	ERSQ	BDI-II follow-up	$\beta = -.55^*$	$\beta = -.62^{**}$	$\beta = .16$	$\beta = .34^a$	$\beta = .53^*$	18
Amygdala activity	DAS	BDI-II post	$\beta = -.01$	$\beta = .62^{**}$	$\beta = .51^{**}$	$\beta = -.006$	$\beta = .52^*$	20
Amygdala activity	DAS	BDI-II follow-up	$\beta = .10$	$\beta = .38$	$\beta = .44$	$\beta = .04$	$\beta = .53^*$	17

Note. Amygdala activity = mean beta values of 6 mm right amygdala sphere, M and DV = residualized gain scores. β = standardized regression coefficients. * $P < .05$. ** $P < .01$. ^a Significant point estimate ($P < .05$).

Discussion

The current study examined the role of amygdala and striatal response after confrontation with individualized self-critical stimuli in unmedicated depressed patients and healthy control participants. Additionally, the potential of these subcortical activations as biomarkers of CBT-outcome prediction in concert with likely psychological change mechanisms was investigated.

Depressed vs. healthy

According to our hypothesis, patients showed enhanced activity compared to healthy control subjects in the left amygdala, the bilateral putamen, and the right caudate nucleus. Hyperactivity in the amygdala and striatal regions has previously been reported after emotional activation, potentially indicating an altered neural circuitry involved in emotional processing (Drevets et al., 2008; Fitzgerald et al., 2008; Kessler et al., 2011).

Notably, the activation pattern found in this study is comparable to recent findings on group differences using individualized interpersonal and depression-specific stimuli (Kessler et al., 2011). As in the current study, the authors found no group differences in prefrontal structures but enhanced activity in the amygdala and the ventral striatum. The present results support the usability of more ecologically valid task-designs using individualized stimuli for the study of abnormal subcortical responses in MDE patients.

On the cortical level, we found enhanced activity in MDE patients in a distributed network of the bilateral occipital cortex, mainly in higher-order visual areas, extending to the bilateral fusiform gyrus. Emotional induction utilizing visual stimuli likely activates the occipital cortex (Phan et al., 2002) and enhanced activity in these regions might be driven by hyperactivity of the amygdala, which has strong anatomical connections to visual areas (Amaral et al., 2003).

Responders vs. non-responders

Therapy non-responders showed increased neural activity in the right amygdala during confrontation with self-critical material when compared to responders. In addition, brain activity in this region correlated negatively with CBT outcome. These results indicate that there might be a subgroup of MDE patients with enhanced amygdala activity in response to emotional stimuli, predicting poorer CBT outcome. Ruling out alternative explanations of the observed differences

between responders and non-responders, these groups did not differ regarding sex distribution, age, marital status, highest educational level, single or recurrent episode, chronicity, comorbid anxiety disorder, or baseline symptom severity. Therefore, future research may examine the risk factors of insufficient treatment response that are associated with elevated amygdala response in more detail. Remarkably, Bryant and colleagues (Bryant et al., 2008) reported a similar association between amygdala activity at baseline and insufficient treatment response in PTSD patients, raising the question of amygdala hyper-reactivity being a trans-diagnostic risk factor of therapy non-response.

Mechanisms of change

Mediation analyses showed that the negative relationship between right amygdala activation and change in depressive symptoms during therapy can be explained by improvement of emotion-regulation skills. Given that there was no mediation for change in dysfunctional attitudes, the specificity of this finding for emotional changes (Kazdin, 2007) is highlighted. Thus, considering these results, we hypothesize that high amygdala activation by individualized self-critical stimuli at baseline might hamper a patient's readiness to learn new emotion-regulation skills. In support of this hypothesis, a recent study demonstrated that adding emotion-regulation training to CBT for depressed inpatients improved treatment outcome (Berking et al., 2013).

Clinical implications and limitations

To our knowledge, this is the first study to examine the potential change mechanisms underlying a biomarker-outcome association. As a potential clinical consequence of our findings, therapists may identify patients who might benefit from an initial training of emotion-regulation skills before engaging in emotionally challenging interventions in the course of psychotherapy. As an alternative to compensating for skill deficits, therapists might also search for individual strengths to build upon when dealing with challenging emotions, such as memories of previously mastered challenges or interpersonal resources. Along these lines, a recent study has reported better outcomes in personalizing treatment to patients' relative strengths than to patients' relative deficits (Cheavens et al., 2012).

If replicated, our findings may also stimulate further research into ways of regularizing amygdala responses more directly, e.g., by targeting cortico-limbic circuits with deep brain stimulation

(Johansen-Berg et al., 2008) or medication with antidepressants (Sheline et al., 2001).

However, because of the small sample size our results must be regarded as preliminary. Moreover, several important questions remain unanswered and should be addressed in future studies. Whereas this study identified a possible link between neural activity at baseline and a psychological mechanism of change, it is still unclear how exactly amygdala hyperactivity might impede the improvement of emotion-regulation skills. One explanation may be that overly strong emotions are experienced as distracting and overwhelming, and consequent avoidance of displeasing emotions might impede or even prevent emotional change. Methodologically, we recommend the use of in-session assessments to further clarify the links between neural predictors and process-outcome relationships in psychotherapy. Overall, this interdisciplinary research strategy holds great promise for further tailoring the treatment of depressed patients in service of better outcomes.

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Supplementary material:

S1: Cortical brain areas with enhanced activity in MDE patients compared to control participants.

S2: Details of responder analysis with covariates.

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Supplementary material

S1 Cortical brain areas with enhanced activity in MDE patients compared to control participants.

Anatomical region	Hemisphere	Cluster size (voxel)	t (df 49)	P corrected (Cluster-level)	MNI coordinates x y z (mm)		
Fusiform	Right	236	4.47	0.040	40	-54	-18
	Right		4.46		40	-44	-18
	Right		3.62		30	-62	-16
Occipital inferior	Left	1632	5.98	<0.001	-28	-76	-6
Fusiform	Left		5.70		-36	-58	-16
	Left		4.72		-36	-44	-12
Precentral	Right	246	4.74	0.027	46	-6	42
	Right		3.32		42	-2	56
Cuneus	Right	412	4.29	0.004	20	-68	36
Occipital superior	Right		3.69		28	-78	20
Occipital middle	Right		3.67		32	-68	16

Note. Clusters significant at $P < 0.05$ ($\kappa > 10$) on whole brain level after statistical correction (FWE correction at cluster level, $P < 0.05$) are reported. Multiple peaks within the same label are shown on subsequent lines. Regions are labeled according to the AAL-atlas.

S2 Details of the responder analysis including covariates.

Covariate (pre)	Anatomical region	MNI coordinates x y z (mm)	t (df 18)	Cluster size (voxel)
BDI-II	Right Amygdala	24 2 -20	4.12	22
STAI trait	Right Amygdala	26 0 -22	4.65	40
Comorbid anxiety	Right Amygdala	26 0 -22	4.80	38

Note. Clusters significant at $P < 0.001$ unc. ($\kappa > 10$). Regions are labeled according to the AAL-atlas

3. Discussion

In the following, the results of the three studies included in this work will be discussed as a whole. The aim is to draw general conclusions from an integrative perspective, to discuss possible clinical implications, and finally, to develop ideas for directions of future research based on the current findings.

The three studies presented in Chapter 2 all aimed at studying emotional processing in depression from different perspectives. The first study (manuscript I) underpinned the role of emotional processing during psychotherapy for depression as an important mechanism of change by deliberately fostering emotional processing in standard CBT for depression. The second study (manuscript II) was designed to test how far confrontation with individualized self-critical stimuli acts as a valid challenge to study emotional and cognitive processes using fMRI methods. In the last study (manuscript III) we went one step further by investigating altered neural processing in brain structures associated with emotional processing during confrontation with self-critical material in depressed patients as opposed to healthy subjects. Moreover, we tested the potential of activity in a certain brain structure, i.e. the amygdala, as a possible biomarker for treatment response in psychotherapy against depression.

3.1 Fostering emotional processing in psychotherapy for depression

Emotional processing is discussed to be an important mechanism of change during psychotherapy with depressed patients (Greenberg & Watson, 2006). Existing research suggests that adding techniques that facilitate clients' experience and expression of emotions may improve the effectiveness of CBT (e.g., Hayes et al., 2005; Hunt et al., 2007; Watson & Bedard, 2006). Thus, the RCT was conducted to compare common CBT (Hautzinger, 2003) with EBCT-R, a novel and adapted theory-based depression treatment that has specifically been developed to foster emotional processing in a CBT context (Hayes et al., 2005).

Results of pre-post analyses (manuscript I) suggest that EBCT-R and CBT are both efficacious with large effects comparable to changes of previous controlled-trials with depressed outpatients (Minami et al., 2007). Furthermore, effect sizes for EBCT-R and CBT were comparable. This is not surprising as existing literature rarely reported differences in efficacy between different forms of psychological therapies (Cuijpers et al., 2008). A feasible explanation might be that most effects of psychological treatments operate through common, nonspecific factors (e.g., the therapeutic alliance, a clear rationale, the patients' belief in a specific treatment) and not particularly through different techniques. Another possible, yet not exclusive explanation might also be that the same outcome is achieved through different, therapy-specific mechanisms resulting in similar outcomes (Butler & Strupp, 1986). Therefore, we were interested in diverging processes of change between the two variants of CBT. Process variables were obtained by assessing patient's experiences through brief post-session questionnaires. Remarkably, results showed no difference in patient-reported emotional processing between the two treatments in the exposure phase (phase 2). However, only emotional processing in the exposure phase of EBCT-R predicted better therapy outcome after treatments ended. These findings suggest that EBCT-R might have its effects, as theorized, by facilitating affective engagement and emotional processing that predicts better outcome.

In summary, the trial lends further support to the central role of emotional processing in therapeutic change and suggests that exposure principles might be fruitfully applied in the treatment of depression. Moreover, emotional processing predicted better outcome. The integration of interventions fostering in-session emotional processing might therefore facilitate change in psychotherapy for depression.

3.2 Neural correlates of self-critical stimuli in healthy subjects

On a neural level, we first intended to study the neural correlates of self-criticism in a group of healthy subjects (manuscript II). Using fMRI measurement, we confronted participants with visually presented self-critical stimuli. By applying a design with individualized painful stimuli, we expected to foster emotional processes and subsequent attempts of cognitive control processes. Results showed activity in anterior and posterior midline structures, which are associated with self-referential and autobiographical memory processing. Furthermore, response to self-critical stimuli compared to neutral stimuli yielded an enhanced activation of the hippocampus-amygdala formation and the anterior insula. Both structures have been implicated in the mediation of emotional responses, including emotional arousal, retrieval of emotional past experiences, and the monitoring of internal states (Damasio et al., 2000). Furthermore, during confrontation with self-critical material, healthy participants also recruited an extended lateral and medial frontal brain network possibly in order to apply cognitive emotion regulation strategies, thereby down-regulating subjective emotional experience and amygdala activity (Kalisch, 2009; Kanske et al., 2011; Ochsner & Gross, 2008). These results suggest that a healthy way to deal with harsh self-criticism includes neural processing involving both bottom-up and top-down pathways. Based on previous research suggesting that right superior areas of the frontal cortex might be altered in patients recovered from clinical depression (Hooley et al., 2009; Hooley et al., 2005), we examined the links between potential risk factors and/or protective factors of depression and neural activation in this region. We found a positive association between trait neuroticism, as well as a negative association between self-reported cognitive reappraisal and neural activation in the right superior frontal cortex. This may indicate that highly neurotic yet healthy people require stronger right frontal cortex activation in order to regulate their negative feelings associated with harsh self-criticism. Conversely, people using cognitive reappraisal strategies more frequently and more successfully may be able to achieve regulation with less neural effort.

This study confirmed our expectations of self-criticism to be a strong intra-psychic stressor that is suitable for the assessment of associated neural cognitive and emotional responses. On the basis of these results, we were motivated to go one step further trying to uncover potential differential responses to harsh self-critical stimuli in acutely depressed patients using the same successfully tested design (manuscript III).

3.3 Neural correlates of self-critical stimuli in acutely depressed patients

The third study (manuscript III) aimed at investigating neural responses to self-critical material in patients suffering from an acute major depressive episode (MDE). We measured 23 patients before starting a variant of individual CBT for depression lasting 22 sessions. As our previous study (manuscript II) has shown that individualized self-critical stimuli were successful in triggering emotional responses, we were particularly interested in subcortical alterations reflecting bottom-up emotional processing of depressed patients during confrontation with an emotional challenge.

Results revealed that compared to healthy control subjects, depressed patients showed enhanced activity in subcortical regions, namely in the left amygdala and the bilateral ventral striatum. Hyperactivity in the amygdala and the striatum has been reported after emotional activation, potentially indicating an altered neural circuitry involved in emotional processing (Drevets, Price, & Furey, 2008). The amygdala plays a central role in various aspects of affect processing and mood regulation by its rich anatomical connections to other limbic and cortical regions. The key function of the amygdala is the processing of emotionally relevant sensory input signals and emotional memories by interacting with other regions such as sensory cortices, the thalamus, and the hippocampus. Moreover, the amygdala is connected with central autonomic structures involved in expressing emotions (Barbas, 2000; Drevets, 2003). The striatum as a component of the basal ganglia has consistently displayed increased hemodynamic activity in depression after induction of negative affect (Fitzgerald et al., 2008). Through rich interconnections with limbic structures, including the amygdala, and several prefrontal areas, the basal ganglia participate in multiple cortical-subcortical loops engaged in reward, punishment, affect, and motivation (Camara, Rodriguez-Fornells, & Münte, 2008). Unlike several studies investigating neural differences between acutely depressed patients and healthy controls using imaging methods (see Fitzgerald et al., 2006; Hamilton et al., 2012; Koenigs & Grafman, 2009 for overviews), we did not detect any statistically significant differences between depressed patients and healthy control participants regarding frontal activity indicating altered cognitive control processes. However, as mentioned before, our results are highly comparable with findings of a previous study that also used individualized and depression-specific stimuli (Kessler et al., 2011). As in the present study, the authors found no group differences in prefrontal brain structures when comparing neural activation of acutely depressed patients with activation of a healthy

control group. One explanation for these findings might be the task designs using individualized and emotionally painful stimuli that were not based on any cognitive performance. Thus, as prefrontal abnormalities might mainly be responsible for the cognitive deficits in depression (Harvey et al., 2005), it seems not surprising that in our study no differences in prefrontal areas were detected.

Taken together, these results further support the potential of more ecologically valid task-designs using individualized stimulus material for the study of abnormal subcortical responses in MDD.

3.4 Strong amygdala response predicts outcome in psychotherapy for depression

After investigating differences in subcortical structures between depressed patients and healthy participants, we were interested in potential pre-therapy neural activities differentiating between therapy responders and non-responders, as well as the potential psychological mechanisms underlying this association. Although psychological treatment for depression is efficacious, response rates are still far from satisfying and a better understanding of potential neural mechanisms underlying outcome prediction may improve the prediction of treatment response of psychotherapy and medication therapy. As previous research has shown inconsistent findings (Fu, Steiner, & Costafreda, 2013) it is still an unresolved issue whether baseline neural activity to emotional stimuli has the potential to be a valid predictor of treatment outcome in psychotherapy for depression. In the last study, we tried to identify reliable neural predictors for successful CBT outcome. We then went one step further by setting out to study the mechanisms underlying these potential predictors (manuscript III).

Comparing neural activity during an emotional challenge with self-critical material between subsequent therapy responders and therapy non-responders yielded differential activity in the right amygdala, with non-responders showing amygdala hyperactivity. Interestingly, therapy responders and non-responders did not differ in socio-demographic variables, depression severity, course of depression, or other psychometric variables, such as trait anxiety before starting the treatment. Additionally, brain activity in the right amygdala was negatively correlated with CBT outcome. Previous research examining amygdala reactivity as a predictor of treatment response has revealed mixed results (Fu, Steiner, & Costafreda, 2013). Remarkably,

another research group has reported a similar association in patients suffering from PTSD (Bryant et al., 2008). The authors have reported that patients who showed an enhanced amygdala activity during the processing of masked fearful faces before starting a CBT showed insufficient therapy response. If further replicated, the current finding might augment additional evidence for abnormally enhanced amygdala reactivity being a trans-diagnostic risk factor of psychotherapy non-response.

As described above, CBT requires activation of distributed cognitive-emotional networks to achieve lasting changes. However, there also needs to be adequate management of the arousal elicited in therapy (Greenberg, 2004; Samoilov & Goldfried, 2000).

One might therefore argue that the more intense amygdala activity during CBT becomes, the more regulation capacities of overwhelming emotions would be needed from the individual to adequately cope with this emotional challenge. Consequently, the less emotion regulation capacities the individual has, the less he or she might be able to down-regulate overwhelming emotions and cope with a particular emotional challenge. Johnstone and colleagues' finding (2007) that depressed patients showed a positive association between the ventromedial prefrontal cortex and the amygdala when actively down-regulating their emotions, seems to fit into this picture. Concurrently, the activation of frontal control regions had dampening effects on amygdala activity in healthy control participants. The authors suggested that for patients showing such an impeded prefrontal-amygdala circuitry, psychotherapy might not be as effective as for other individuals for whom the circuitry is functionally more intact.

Taken together, the results suggest that patients with abnormally enhanced amygdala reactivity to emotional stimuli might not do as well in psychotherapy for depression as their frontal control circuitries might be disturbed, leading to exaggerated limbic responses. However, it still remains unclear which psychological mechanisms might underlie the association between strong amygdala response and poor therapy outcome.

3.5 Emotional-skill acquisition mediates the association between strong amygdala response and poor therapy outcome

We studied the change in dysfunctional attitudes and emotion-regulation skills as theoretically derived and empirically supported cognitive and emotional mechanisms of change. These

mechanisms might be compromised by abnormally enhanced amygdala reactivity, thereby impeding successful change during psychotherapy. Mediation analyses examining the mechanisms potentially underlying the association between strong right amygdala response and poor response to CBT showed full mediation of the emotional change mechanism but no mediation of the cognitive change mechanism. In support of these findings, we also found full mediation for change in emotion-regulation skills until three months after therapy termination. These findings suggest that high amygdala activity at baseline might diminish the patients' readiness to learn new emotion-regulation skills or improve existing ones. In line with this hypothesis, a recent study demonstrated that adding systematic emotion-regulation training to routine CBT for depressed inpatients improved treatment outcome. Participants in the condition that integrated a training of emotional skills demonstrated a significantly greater reduction in response and remission rates. Furthermore, greater reduction of negative affect, as well as greater increase of well-being and emotion regulation skills were measured (Berking et al., 2013).

To sum up, emotion regulation might be a key component of successful CBT in depression. On a neural level, abnormally strong response of the amygdala might impede emotional processing thereby hampering successful change during CBT.

3.6 Integration of findings

In the following section I would like to integrate and discuss the findings in reference to the questions asked at the very beginning of this work:

- Does fostered emotional processing enhance response rates of psychotherapy for depression?
- Is emotional processing linked to psychotherapy outcome?
- Is self-criticism a valuable trigger for studying cognitive and emotional neural responses?
- Do acutely depressed patients show alterations in cognitive and emotional information processing to self-critical stimuli compared to healthy control participants?
- Are alterations in emotional information processing of depressed patients linked to psychotherapy outcome?
- Which psychological processes are involved in the association between fMRI activity and treatment response?

Although CBT and the EBCT-R did not differ in efficacy post treatment, the randomized-controlled study confirmed the assumption that emotional processing in the form of awareness/arousal of emotions, enhancement of emotion-regulation, and subsequent reflection on emotions during psychotherapy sessions is positively related to therapy outcome.

On a neural level, individualized self-criticism proved to be a useful stressor for provoking emotional (and cognitive) brain responses in healthy and acutely depressed individuals. For future research, the current paradigm might even be a suitable task design for measuring brain activity over the course of psychotherapy for depression as self-critical aspects are specifically targeted. Second, the current work has shown that neurophysiological brain response to emotional stimuli might be altered in depressed patients with enhanced subcortical reactivity in the amygdala and the ventral striatum possibly underlying insufficient frontal control processes.

Lasting change of solid emotional schemas crucially requires activation of the emotional brain network. However, as discussed before, experienced arousal might not be productive if a patient solely experiences strong emotions without working on the emotional significance in therapy (Samoilov & Goldfried, 2000). Accordingly, drowning in emotions might even be counterproductive for successful change. In line with this, we could show that abnormally enhanced amygdala reactivity results in poor therapy response. Moreover, the amount of emotional-skill acquisition during the process of therapy fully mediated the relationship between strong amygdala response and poor therapy outcome, suggesting that patients with extremely strong amygdala response have difficulties in learning new emotion regulation skills or building upon existing ones. So far, we are not able to explain if overly strong amygdala response is genetically determined and/or is based on past experiences and learning processes. However, we speculate that uncontrollable neurophysiological hyper-reactivity is associated with past problems of regulating own emotions successfully and that affected patients may have a harder time to engage in therapeutic work that is affectively charged with negative emotions. A common way to regulate emotions being practiced by many is to simply avoid them. Hayes and colleagues (1996) described a type of emotion regulation that they called experiential avoidance. Experiential avoidance includes avoidance of emotions, thoughts, images, memories, and physical sensations. They also propose that emotional exposure involves decreasing avoidance and targeting the fear of strong emotions. With a reduction in fear, the negative self-schema can then be dislodged and opened to new information (Hayes et al., 2005; Hayes et al., 2007). It therefore might be that patients with amygdala hyperactivity may tend to feel overwhelmed by

their emotions. As a result, they do not engage in emotional processing and fail to change rigid emotional patterns. However, this hypothesis is still speculative and needs to be tested in future research.

Taken together, the results from psychotherapy process research and from the fMRI findings converge on the notion that disturbed processing of emotions and dealing productively with them might be a key factor of successful therapy outcome in psychotherapy with depressed patients.

3.7 Implications for clinical practice

First of all, the current thesis underlines the importance of acknowledging the central role of emotional processes in psychotherapy with depressed patients. Our results should encourage psychotherapists to integrate specific exposure techniques in standard CBT procedures in order to foster emotional processing. Moreover, we could also show that even rather inexperienced therapists accomplished very good outcomes practicing an integrative therapy.

As discussed before, patients with high levels of self-criticism represent a challenge for practicing therapists. Our results indicate that in healthy participants on a neural level, self-criticism involves the activation of structures that generally relate to cognitive and emotional processing. In addition, depressed patients showed altered responses in brain structures that are crucial for emotional bottom-up processing as compared to healthy control participants. We therefore tentatively conclude that acutely depressed patients respond to individualized self-criticism with an abnormally enhanced emotional reaction that might not be sufficiently controlled through efforts of cognitive control mechanisms. In addition to interventions that strengthen cognitive control skills, as typically implemented in cognitive therapies, our results suggest that clinicians might achieve even better and more sustainable results if their interventions target emotional bottom-up processing additionally more directly. Thus, working with patients' self-views using emotion-focused interventions, for example two-chair technique, might be particularly beneficial in highly self-critical individuals. However, this supposition remains to be investigated in future research.

Our current results suggest that it might be important to adapt treatments for patients with overly strong amygdala responses to emotional stimuli. There might be different ways to approach this.

On a psychological level, these patients might benefit from an initial training of emotion-regulation skills before engaging in emotionally challenging interventions later in therapy (Berking et al., 2013). With respect to this, we showed that improvement of cognitive reappraisal strategies was associated with lesser effort of lateral frontal brain regions in order to regulate unpleasant feelings. We speculated before that avoidance of overly strong emotional reactions might play an important role. Following this line of thought, it might be crucial for these patients to learn that they have the power to withstand unpleasant emotions and that they are capable to stop fearing strong emotions and can overcome avoidance so that they feel ready to engage in emotionally challenging interventions in the course of treatment. The concept of mindfulness views emotions as entities, which we can engage in, without needing to avoid or become entangled (Bishop et al., 2004). Training of mindfulness techniques early in therapy might enhance the patient's expectancy of being able to deal with strong negative emotions.

As patients differ in the degree of individual strengths and deficits at the outset of therapy, therapists may develop a personalized therapy plan to work on reducing relative deficits and/or to build upon pre-existing strengths. We just proposed strategies for reducing deficits in emotion regulation or regarding avoidance of negative experiences as an associated maladaptive coping strategy. As an alternative or in addition to compensating for skill deficits, therapists might also search for individual strengths to build upon when dealing with challenging emotions, such as memories of previously mastered challenges or interpersonal resources. In line with this suggestion, Cheavens and colleagues (2012) tested the approaches of compensation (for deficits) and capitalization (focus on personal strengths) as alternatives for the individualization of treatments for depression. Following one or the other approach, the authors reported better outcomes in personalizing treatment to patients' relative strengths than to patients' relative deficits. We therefore argue that whereas treating patients' deficits is essential, it also pays to focus on the individuals' strengths.

On a biological level, patients with amygdala hyperactivity in response to emotional stimuli may profit from a combined psychopharmacological and psychotherapeutic treatment. Both, psychotherapy and antidepressant medication are thought to affect limbic and prefrontal circuitry, although the mechanisms of action differ. While an important pathway of down-

regulating limbic regions during cognitive psychotherapy is fostering inhibition through increased engagement of frontal areas, antidepressants might target limbic regions more directly (Disner et al., 2011). A previous study has shown that treatment with the antidepressant sertraline, a selective serotonin reuptake inhibitor (SSRI), during eight weeks led to normalization of enhanced amygdala response to masked emotional faces in depressed patients (Sheline et al., 2001). Another study reported a reduction in amygdala activation in depressed patients during processing of emotional faces after three weeks of antidepressant medication with the SSRI escitalopram compared to placebo (Arce et al., 2008). The effects of SSRIs in affective disorders are likely to be the result of the interaction between serotonin pathways with the cortical-subcortical circuits involved in the processing of emotional stimuli (Fu et al., 2004). As antidepressants seem to suppress symptoms rather than to be curative (Hollon, Thase, & Markowitz, 2002) patients showing enhanced limbic reactions might especially profit from a combined psychological-pharmacological therapy. Additionally, deep-brain stimulation targeting cortical-subcortical circuits (Bewernick et al., 2010; Johansen-Berg et al., 2008; Kennedy et al., 2011) has shown promise in recent clinical trials despite the uncertainty of the precise mechanisms underlying its efficacy. However, it might be a valuable method for down-regulating amygdala activity more directly. Especially treatment-resistant patients that go on to suffer from debilitating symptoms after treatment with pharmacotherapy and psychotherapy might respond to deep-brain stimulation (Bewernick et al., 2010). Moreover, recent research proposed neurofeedback based on electroencephalography or real-time fMRI as a promising approach for non-invasive modulation of human brain activity. Neurofeedback helps individuals gain control over subtle brain activity fluctuations through real-time feedback. A recent study has shown that after a training, healthy subjects were able to regulate their blood-oxygen-level-dependent (BOLD) fMRI activation in the left amygdala through an enhancement of the functional connectivity between the left amygdala and regions of the prefrontal cortex (Zotev et al., 2013).

Taken together, the use of psychological and neurophysiological approaches to enhance response rates is still in its infancy but step by step research in this field might provide evidence for how to refine treatments so that they can be delivered more effectively and efficiently.

3.8 Limitations and directions for future research

From a research perspective, the findings contribute to a better understanding of neural and psychological mechanisms associated with emotional processing before and during psychotherapy with depressed patients and its association with treatment response. However, numerous questions still remain unanswered and several limitations deserve to be mentioned here.

A crucial limitation to mention here is the small sample size of the prediction analyses of our sample. On account of this, the reported results have to be viewed as preliminary. Given that also previous studies had similar sample sizes (see Fu, Steiner, & Costafreda, 2013 for an overview), it is necessary that future research will examine larger samples that would allow to detect smaller effects. Considering that there is some evidence that hyperactivity of the amygdala might also impede successful therapy in PTSD (Bryant et al., 2008), future research is probably well advised to consider amygdala hyperactivity as a trans-diagnostic factor.

Nevertheless, if replicated, the clinical implications of our fMRI findings regarding treatment prediction are substantial. Understanding the neural differences between patients who do or do not respond to a specific form of psychotherapy will, on one hand, clarify the biological mechanisms going along with psychological changes. On the other hand, such an understanding will also advance the capacity to match treatments to different patients. Aptitude-treatment interaction methods (Snow, 1991) are especially designed to investigate the relationship between differentially moderating variables in different forms of treatments. Stulz and colleagues (2014) recently investigated aptitude-treatment interaction effects between patient baseline characteristics (aptitudes) and process analyses of therapy sessions in psychooncological interventions. They could show that patients with high emotional stress did best when the therapy reduced arousal. On the other side, patients with lower emotional distress benefited most if therapists emphasized arousal induction. These findings may help therapists to make differential treatment decisions at the beginning of psychooncological interventions. Although there is growing evidence for empirically validated approaches to individual treatment selection (Hamilton & Dobson, 2002; Norcross & Wampold, 2011; Watzke et al., 2012), patient characteristics only make a modest contribution to treatment outcome and future research needs to consider the impact of other potential factors (Carter et al., 2011). As a comparatively recent research strategy, functional neuroimaging has also shown significant potential in the

development of prognostic markers of clinical response (Fu, Steiner, & Costafreda, 2013). However, in the long run it seems unrealistic to scan every patient prior to treatment selection. Hence, further research would profit from large, naturalistic studies with a high degree of variability in relevant theoretically derived predictor and mediator variables that might be associated with enhanced amygdala reactivity. Most probably, prognostic patient variables interact in complex patterns of causal relationships.

Regarding the fMRI analyses, we discussed the possibility that enhanced limbic response of the patient group might not only be due to enhanced bottom-up activity but also that top-down control did not work well enough. However, we did not study functional or structural connectivity between frontal brain areas and the limbic system. We therefore highly recommend studying connectivity during self-critical processing but also during episodes of rest.

Using self-criticism as a trigger for cognitive-emotional responses holds the advantage that self-critical thinking is specifically targeted during CBT and EFT based interventions. Hence it would be promising to assess neural changes over time. Methodologically, we strongly recommend the use of longitudinal designs with more imaging sessions and follow-up periods to investigate sustainability of the reported effects. Imaging assessment should further be supported by the use of session-by-session assessments to clarify the links between neural predictors and process-outcome relationships of psychotherapy for depression. In the current work we used variation of emotional skills and dysfunctional cognitive attitudes from pre- to post-treatment as variables of change. However, we suggest that the use of session-by-session assessments of cognitive and emotional change might be a superior way to gain knowledge about neurophysiological-psychological relationships over time.

It is my hope that the well-being of depressed patients will be enhanced by pursuing this path and building up on the present insights.

3.9 References

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Curriculum Vitae

Nadja Ilona Dörig

PERSONAL PROFILE

Address	Nordstrasse 278, 8037 Zurich, Switzerland
E-Mail	nadja.doerig@psychologie.uzh.ch
Date of birth	17.12.1983
Place of birth	Zurich, Switzerland
Nationality	Swiss

EDUCATION

2010 – present	Psychotherapy Training in Cognitive Behavioral Therapy and Behavioral Medicine, University of Zurich, Switzerland
2010 – 2014	Ph.D.-Studies, University of Zurich Section of Psychology, Psychotherapy of Affective Disorders, University of Zurich, Switzerland Cumulative Thesis: The Role of Emotional Processing in Psychotherapy for Depression: An Integrative Neurophysiological-Psychological Approach Advisory Board: Prof. Dr. M. Grosse Holtforth, Prof. Dr. B. B. Quednow, and Prof. Dr. B. Rasch
2011 – 2014	International Ph.D. Program in Neuroscience, Neuroscience Center Zurich (ZNZ)
2003 – 2009	Studies in Psychology, University of Zurich, Switzerland Master of Science, University of Zurich Specialization: Neuropsychology Minor subjects: Biology, Psychopathology Thesis: MDMA Consumption and the Serotonergic System: Effects of a Serotonergic Challenge on Memory Function in Ecstasy-Users
1996 – 2002	Gymnasium Hohe Promenade Zurich, Switzerland Matura, Zurich, Switzerland
1990 – 1996	Primary School Rueterwies Zollikerberg, Switzerland

ADDITIONAL RESEARCH / CLINICAL EXPERIENCE

2012 – present	Working as a psychotherapist in the Ambulatory for Cognitive Behavioral Therapy and Behavioral Medicine, University of Zurich
2012 – present	Working as a psychotherapist in a research trial of psychotherapy for generalized anxiety disorder, University of Zurich
2010 – 2013	Working as a psychotherapist in a research trial of psychotherapy for depression, University of Zurich
09/2007 – 09/2008	Research internship (12 months, 40%), Experimental and Clinical Pharmacopsychology, Psychiatric Hospital, University of Zurich
04/2007 – 09/2007	Clinical internship (4 months, 100%), Psychiatric Hospital, University of Zurich
12/2006 – 01/2007	Student research assistant (150 hours) for EEG-measurements, Department of Neuropsychology, University of Zurich
09/2006 – 12/2006	Research internship (6 weeks, 100%), Department of Neuropsychology, University of Zurich

PUBLICATIONS

Peer-reviewed Publications

- Doerig, N.**, Schlumpf, Y., Spinelli, S., Späti, J., Brakowski, J., Quednow, B.B., Seifritz, E., & Grosse Holtforth, M. (in press). Neural representation and clinically relevant moderators of individualised self-criticism in healthy subjects. *Social Cognitive and Affective Neuroscience*, DOI: 10.1093/scan/nst123
- Späti, J., Chumbley, J., Brakowski, J., **Dörig, N.**, Grosse Holtforth M, Seifritz E, & Spinelli, S. (accepted). Functional lateralization of the anterior insula during feedback processing. *Human Brain Mapping*.
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Other Publications

- Grosse Holtforth, M., Krieger, T., Altenstein, D., **Dörig, N.** (in press). Expositionsbasierte kognitive Therapie. [Exposure Based Cognitive Therapy] In: T. Teismann (Hrsg.) *Moderne Strömungen der psychotherapeutischen Depressionsbehandlung*. Tübingen: DGVT.
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